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Geriatric Diseases

Evaluation and Management

Springer

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With 90 Figures and 79 Tables

Springer

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ISBN 978-3-319-33433-2 ISBN 978-3-319-33434-9 (eBook)
ISBN 978-3-319-33435-6 (print and electronic bundle)
https://doi.org/10.1007/978-3-319-33434-9

Library of Congress Control Number: 2017964114

Printed on acid-free paper

This Springer imprint is published by the registered company Springer International Publishing AG part of Springer Nature
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To our wives Rajarajeswari, Gowrie and Danielle

Preface

Many developed countries have experienced ageing demographics since the early 1900s, especially in the oldest old, the ones over 85. This trend of increased longevity showed little signs of abatement thus far, but with the increased prevalence of lifestyle diseases such as obesity, type II diabetes and hypertension, some had predicted that it will slow or may even reverse.

Ageing is associated with a multitude of physiological changes and a prevalence of multiple co-morbidities. This often leads to atypical presentations of common diseases. For example, it is common for an infective illness to present with falls, cognitive or functional decline. It is also known that the age of onset can lead to different disease presentation as in the case of late-onset Parkinson's disease, where the typical resting tremor is often absent. It is therefore important for clinicians managing older persons to have an acute awareness of the way that age-related physiological changes and co-existing co-morbidities can influence the way an older person presents.

Geriatric Medicine: Evaluation and Management provides a comprehensive overview of the *importance of age of onset on the presentation of common diseases in the elderly.* Apart from providing intense information on a given subject, it also provides means for self-assessment with a combination of multiple choice, short answer and extended matching questions which are based on the text. Interesting short cases are also included. The extensive use of tables and figures throughout the book and a box for key points at the end of each part should be a great assistance to time-poor readers.

The book contains 21 parts arranged by organ system and is structured to cover the specific clinical sub-specialities with emphasis on the age at onset. They are divided into introduction, clinical expression followed by diagnosis and treatment. Many parts follow a common pattern with headings and subheadings. The text offers the primary care physicians, junior doctors, medical undergraduates, specialist nurses and others working in aged-care settings a systematic approach to geriatric medicine. The book we believe will be a companion to the one published earlier, by the same authors *Diseases in the Elderly: Age-Related Changes and Pathophysiology.*

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Acknowledgements

We thank Mr. Luke Elias (Physical Medicine), Dr. Duncan Guy (Cardiology), Dr. Logan Kanagaratnam (Cardiology), Prof. Arumugam Manoharan (Haematology), Prof. Mahendra Somasunderam (Neurology), Dr. J. Sarks (Ophthalmology), Dr. A. PunniaMoorthy (Oral and Maxillofacial) for their help in many ways. A special thanks to Assoc. Prof. WM Amoaku (University of Nottingham), Dr. Derek Davies (Dermatology), Prof. Nicholas Manolios (The University of Sydney), Dr. Thiaga Nadaraja (ENT) and Dr. P. Nithianandan (Ophthalmology) for kindly providing numerous figures, and Mr. Yogan Nagaratnam, Mr. Panjan Nagaratnam (for photographs), Sai Aditiya Nagaratnam, Nathan Nagaratnam and Manisha Nagaratnam for their assistance.

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Continuous development and research in the fields of medicine, science technology and health care result in ongoing changes in the domains of clinical practice as evidence continues to evolve rapidly. We have taken reasonable care and effort to provide materials which are current, accurate and balanced at the time of publication.

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We have acknowledged the sources and works of the cited sites at the appropriate locations in the text and references. We have used the source materials in the sense of fair use and extend our apology for any oversight. Readers are advised to cross-reference and confirm points relevant to them.

Contents

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Kujan Nagaratnam, MBBS (UNSW), FRACP, graduated in Medicine from the University of New South Wales in 1988. He did his internal medical training and advanced training in Geriatric Medicine and Stroke Medicine at Westmead and Royal Prince Alfred Hospitals, Sydney. He obtained his Fellowship of the Royal Australasian College of Physicians (FRACP) in 1997. He held Senior Staff Specialist appointments in General, Geriatric Medicine and Stroke Medicine at Westmead Hospital and Blacktown-Mt Druitt Hospitals until 2012. He is also Visiting Consultant Physician at the Norwest Private and Westmead Private Hospitals in Sydney. He is currently the Chairman and Head of the Department of Geriatric Medicine and Stroke Medicine, Norwest Private Hospital, Sydney. His academic interests include teaching both undergraduate and postgraduate medical students. He is a Clinical Senior Lecturer in Medicine at the University of Sydney. His special interests are stroke medicine, cognitive impairment and dementia, neurological diseases in the elderly and post-operative medical management of elderly patients.

Gary Cheuk, MBBS (UNSW), FRACP, graduated from the University of New South Wales in 1985 with honours. He commenced basic physician training in Dunedin (New Zealand) and St George Hospital (Sydney). He underwent advanced training in Geriatric Medicine at Concord and Westmead

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Part I

Cardiovascular Diseases in the Elderly

With the increase in life expectancy, more so in the developed countries, there will be an increasing number of elderly with cardiovascular disease (CVD). Age is the most important factor in cardiovascular risk scores. With increasing age there are alterations in structure and function of the heart and vasculature. Part I reviews the more important cardiac and vascular diseases. Heart failure is largely a disease of the elderly and is the major cause of disability. Heart failure survival is not appreciably improving. With the increase in the prevalence of heart failure in the elderly it is a major public health problem. As the population ages, there will be an increase in prevalence and severity of cardiac arrhythmias. The older patients are at high risk of contracting infective endocarditis due to the use of inbody cardiac devices. Coronary artery disease (CAD) is the most common form of heart disease in the world today and its prevalence increases with age. There is an increase in the number of elderly patients affected by valvular heart diseases, which is a significant cause of morbidity and mortality. Hypertension is among the leading cause of disease and death with significant evidence that good control is associated with marked reduction on risk of heart disease, morbidity, and mortality. Atherosclerosis is by far the commonest pathological feature of PAD and accounts for more than 80% of peripheral arterial disease.

Heart Failure

1

Contents

Abstract

This chapter provides an overview of heart failure, prevalence and mechanisms followed by an update on the clinical management. The prevalence heart failure is likely to increase over the next few decades with the increase in world population and in over 65 years. With increasing age, there are alterations in structure and function of the heart and vasculature which may eventually affect the cardiovascular performance. Age is the most important factor in cardiovascular risk scores. Heart failure is largely a disease of the elderly and is the major cause of disability in the elderly. The elderly are inclined to developing heart failure as a result of age-related changes in the

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_1

cardiovascular system and high prevalence of coronary heart disease and hypertension. Older patients could present with confusion, sleeplessness, agitation, depression, loss of appetite or nausea, weakness, cough and breathlessness on exertion. The management of heart failure is dictated by the mechanism underlying the heart failure. Patients with systolic heart failure had higher death rates than patients with diastolic heart failure although the death rates in the latter group were still much higher than those without heart failure. There have been considerable advances in the treatment of heart failure, yet the mortality remains high at 50% after 5 years. The case for heart failure prevention is very strong. The impact of heart failure will significantly increase with the population ageing and poses a heavy burden on the healthcare system.

Keywords

Heart failure · Systolic heart failure · Diastolic heart failure · Impact of heart failure · B-type natriuretic peptide (BNP) · Cardiovascular ageing

Introduction

With the increase in life expectancy more so in the developed countries, there will be an increasing number of elderly people, and this trend will continue. The oldest old (<85 years) are the fastest growing segment of the population, and in the United States, they constitute 27% of this older segment of the population [1]. What this means is there will be an increase in the number of elderly people with cardiovascular disease (CVD). Age is the most important factor in cardiovascular risk scores [2, 3]. In the United States, 82% of all deaths were attributed to CVD in the adults aged >65 years [4]. CVD remains the most significant cause of death in the United Kingdom [5]. With increasing age, there are alterations in structure and function of the heart and vasculature which may eventually affect the cardiovascular performance [6]. It is likely that cardiovascular ageing involves mechanisms which are the result of a variety of insults such as oxidative stress, inflammation, non-enzymatic glycation and changes in the cardiovascular gene [7].

Heart failure is largely a disease of the elderly [8] and is the major cause of disability in the elderly. Increasing age itself is a risk factor in its development for about half of all heart failures occur in the over 70-year age group [8]. The overall incidence of congestive heart failure increases with age and affects 10% of people over the age of 65 years [9]. In one study of 5,532 men and women over the age of 65 years with average age of 74 years, 5% had heart failure; 45% with heart failure died within 6–7 years compared to 16% without heart failure in the same period [10]. After the age of 65 years, the incidence of heart failure approximates 10 per 1,000 people increasing to 100 per 1,000 people in those over 80 years [11]. The incidence of congestive heart failure among community-dwelling elderly is 7–8% after the age of 75 [12]. In the United States, 5.7 million individuals have heart failure [13]. Improvement in life expectancy of patients with ischaemic heart disease has contributed at least partly to the rise in the prevalence of heart failure with preserved ejection fraction [14], while the death rate remains unchanged [15].

Its prevalence is likely to increase over the next few decades with the increase in world population and in over 65 years. Heart failure affects 10% or more of patients over the age of 80 years with an annual incidence of 20–30 cases per 1,000 persons [16]. In Scotland the prevalence was 7.1 in 1,000 increasing with age to 90.1 in 1,000 among patients more than 85 years, and the incidence of heart failure rose in the age group from 2.0 in 1,000 to 22.4 [17]. Approximately 80% of those hospitalised with heart failure are in the 65 years or more age group. The elderly are inclined to developing chronic heart failure as a result of age-related changes in the cardiovascular system and high prevalence of coronary heart disease and hypertension [18]. There have been considerable advances in the treatment of heart failure, yet the mortality remains high at 50% after 5 years [19].

There is a sharp rise in the prevalence of heart failure in the elderly, but in a significant proportion, the systolic function is normal or near

normal. About 55% [20] to 62% [10] of the patients 65 years and over with heart failure had normal systolic function. In 15% it was borderline or decreased and clearly abnormal in 22% [10]. In another study, over half (55%) had normal left ventricular systolic function, and there was a distinct gender difference, 67% of women had normal systolic function [20, 21] compared to 42% men [21]. Patients with systolic heart failure had higher death rates than patients with diastolic heart failure although the death rates in the latter group were still much higher than those without heart failure [10]. The common causes of heart failure are shown in Box 1.

Box 1 Common Causes of Congestive Heart Failure in the Elderly

Hypertension can lead to systolic and/or diastolic dysfunction.

Coronary artery disease can lead to acute or chronic heart failure.

Cardiomyopathy-hypertrophy, alcohol and viruses are common causes.

Aortic stenosis-calcific, atherosclerotic, degenerative.

Mitral regurgitation: ischaemia, annular, calcification, myxomatous degeneration.

Cor pulmonale: signs of right heart failure.

Senile amyloidosis.

Clinical Manifestations

The presentation of elderly patients with heart failure is often unusual when compared with younger patients. Age-related changes in cardiac structure and function contribute to this pathology. Older patients could present with confusion, sleeplessness, agitation, depression, loss of appetite or nausea, weakness, cough and breathlessness on exertion. The physical examination too could be atypical, for example, the crackles in the lungs are frequently the result of pulmonary disease and the swelling of the ankles can be secondary to malnutrition or venous insufficiency in older people and not indicative of heart failure. Two specific signs of heart failure in older patients are elevation of the jugular venous pressure and/or a third heart sound. Heart failure results in impairment of the functional capacity and quality of life of patients. The degree of effort necessary to bring about symptoms has been used in a system to classify the severity of heart failure by the New York Heart Association (NYHA).

Diagnosis

The signs and symptoms are similar in both systolic heart failure and heart failure-preserved ejection fraction (HF-PEF), and to make a diagnosis, it would be necessary to measure the left ventricular ejection fraction [22, 23]. Heart failure is largely a clinical diagnosis based on a careful history and physical examination and supported by investigations. It is characterised by specific symptoms in the history and signs in the physical examination. Nevertheless making a precise diagnosis can be difficult more so in the elderly. There is no single diagnostic test for cardiac failure for its diagnosis is based on the clinical history and physical examination. Clinicians in a casualty department in an American hospital were uncertain in diagnosis of cardiac failure in 40% of the patients especially in those who presented with dyspnoea and had difficulty in differentiating dyspnoea due to cardiac failure and dyspnoea due to other causes [24].

The electrocardiogram (ECG), chest x-ray, serum electrolytes, urea, creatinine, liver function and thyroid function tests are the usual tests done. Clinical assessment is followed by the assessment of left ventricular function by electrocardiography. A normal ECG for all practical purposes rules out heart failure due to systolic dysfunction [25]. Echocardiography may be necessary in most patients with symptoms and signs of heart failure, breathlessness associated with atrial fibrillation, in those with high risk for left ventricular dysfunction and in those with a murmur and breathlessness. The echocardiography helps to assess left ventricular function and identify the causes of heart failure, for example, valvular, left

ventricular hypertrophy and regional wall abnormalities, suggesting coronary artery disease among others. The information obtained is quantitated to measure left ventricular ejection fraction, evaluate regional wall abnormalities and measure wall thickness and ventricular volumes and dimensions. Doppler measurement of mitral valve inflow profile helps in the diagnosis of diastolic dysfunction.

Echocardiography is rarely available in general practice or smaller emergency departments where patients with early symptoms present. More recently, it had been shown that the estimation of the B-type natriuretic peptide (BNP) and its N-terminal fragment (N-terminal pro-B-type natriuretic peptide (NT pro BNP)) could be a useful tool in the diagnosis of clinical heart failure or in screening for left ventricular systolic dysfunction [26]. BNP is a neurohormone produced by the heart muscles and is released when the heart muscles are overstretched [27]. It is sensitive but not specific for the diagnosis of heart failure [28]. BNP levels are also affected by conditions such as pulmonary embolism, renal failure, obstructive pulmonary disease and cirrhosis of the liver which may lead to moderate elevations of BNP plasma concentrations of 100–400 pg/ml [27]. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and spironolactone have been shown to decrease BNP in parallel with clinical and haemodynamic improvement [27]. The test performance appears to decline with increasing patient age [26]. However it has been found that BNP is not only useful in the diagnosis of heart failure but also in determining the seriousness and likely outcome. In about 20% of the patients however with long-term stable heart failure, normal levels may be seen [27]. Its optimal utility use has yet to be determined [29] in the clinical setting.

Management

The management of heart failure is dictated by the mechanism underlying the heart failure. More than half of the patients over 65 years of age with heart failure have relatively intact left ventricular ejection fraction (LVEF) of >40% and are considered to have left ventricular diastolic dysfunction (HF-PEF) [30]. There is impaired relaxation and reduced compliance ("increased stiffness") of the myocardium. Those individuals with heart failure and a left ventricular ejection fraction of <40% had left ventricular systolic dysfunction (systolic heart failure). The distinction is necessary for specific treatment in one may be inappropriate for the other. There is however a substantial overlap between the two conditions.

The important element in the diagnostic evaluation is to determine the aetiology. The echocardiogram (ECHO) helps not only to determine whether the LVEF is normal or abnormal but also determines whether the left ventricular wall is normal or abnormal and any other structural abnormalities such as valvular abnormalities and pericarditis among others. Coronary heart disease and hypertension are common aetiologies of heart failure in the elderly and often coexist. Valvular heart diseases – aortic stenosis and mitral regurgitation – are also common in the older age groups, whereas hypertrophic cardiomyopathy, non-ischaemic dilated cardiomyopathy and restrictive cardiomyopathy are less common [30]. In the elderly, there is a shift from coronary heart disease to hypertension as the most common aetiology in the development of chronic heart failure, features that distinguish chronic heart failure in the elderly from chronic heart failure in the middle-aged and involving an increasing proportion of women [30]. This is followed by the identification of any precipitant cause for the heart failure such as infection, anaemia, fever, pneumonia, thyrotoxicosis or excessive salt intake and/or excessive alcohol intake and certain non-steroidal anti-inflammatory drugs such as indomethacin and ibuprofen.

Prevention Measures

In the past few years, there has been a shift in emphasis towards prevention in those who are at risk for heart failure. The American College of Cardiology and American Heart Association

(ACC/AHA) in its 2013 Guidelines Update [31] provides revised evidence-based recommendations for further treatment of chronic heart failure. Those at risk for heart failure and those in heart failure were categorised into stages in their development of heart failure. Those at risk for heart failure were divided into two stages A and B. Stage A were those who were at high risk for HF without any structural heart disease or symptoms of HF and included patients with hypertension, atherosclerotic disease, diabetes, obesity and metabolic syndrome and those with a family history of cardiomyopathy and those using cardiotoxins. Stage B were those with structural heart disease but without signs and symptoms of HF, and they included those in Stage A who developed structural heart disease and patients with previous myocardial infarction, asymptomatic valvular disease and left ventricular remodelling (dilatation and/or hypertrophy). Those in heart failure were designated Stages C and D. Stage C embraced all those with known structural heart disease with prior or current symptoms of HF and Stage D patients with refractory HF requiring special interventions.

The case for heart failure prevention is very strong. In the Australian National Vascular Disease Prevention Alliance (NVDPA) guidelines, absolute risk is categorised as low, moderate and high [32]. The absolute risk is calculated as the probability of the stroke, TIA, myocardial infarction, angina, peripheral arterial disease or heart failure within the next 5 years [33]. Regardless of the risk level, individuals should all receive similar lifestyle advice (Box 2), and with moderate risk, drug therapy is considered only if the risk does not decrease in 3–6 months following lifestyle advice [34]. Primary care physicians are in a unique position to initiate preventive interventions in this age group.

Box 2 Modifiable Risk Factors in Preventive Intervention

To keep physically active
To stop smoking
To eat healthy
To reduce alcohol intake and illicit drug use
To control blood pressure (BP <120/80 mmHg)
To reduce weight
To control cholesterol (total cholesterol <5 mmol/L; LDL <3 mmol)
To achieve good glycaemic and blood pressure control in diabetics (HbA1c 6.2–7.5%; BP <130/85 mmHg)

Information sources: Nelson and Doust [34]

Treatment

Heart failure with preserved ejection fraction (HF-PEF) – diastolic heart failure).

The treatment of diastolic heart failure today is still empirical [35]. Because of the steep left ventricular pressure-volume relationship, these patients are very sensitive to diuretics. Care should be taken to avoid hypovolaemia in the use of diuretics and to avoid them unless there is frank pulmonary oedema. Beta-blockers are useful to control the heart rate or maintain atrial contraction and have the advantage of treating underlying hypertension or ischaemia. In the Seniors study, beta-blocker nebivolol was found to reduce hospitalisation due systolic and diastolic heart failure. It has vasodilator properties and is well tolerated and effective in heart failure in the elderly [36]. Alternatively or if the beta-blockers are poorly tolerated or contraindicated, calcium channel blockers (diltiazem or verapamil) which promote ventricular relaxation and heart rate reduction can be used provided there is no systolic dysfunction in which case these agents may reflect myocardial contractility and may lead to promote pulmonary oedema [37]. Angiotensin-converting enzyme (ACE) inhibitors promote the regression of left ventricular hypertrophy and control blood pressure and have been advocated [38]. In diastolic heart failure, ARBs have the potential to decrease morbidity but not mortality [39], and it

has been reported that statin therapy has the ability to decrease mortality [40]. In addition to beta-blockers, calcium antagonists and ACE inhibitors, digoxin and diuretics may play a role [20]. The optimal management of diastolic heart failure is evolving.

Systolic Heart Failure

Specific drug therapy for systolic heart failure can be considered in two categories, namely, (i) agents to improve cardiac function and prognosis based on the evidence that they decrease mortality and morbidity and (ii) agents to relieve symptom [41] such as diuretics, digoxin and restriction of dietary sodium. The former include the ACE inhibitors, angiotensin receptor blockers (ARBs), beta-blockers and spironolactone. Statin therapy is associated with lowering mortality in systolic heart failure [42]. An Algorithm 1 is provided that summarises the approach involved in the management of heart failure.

Drugs Used in Heart Failure

The pharmacotherapy in the elderly is no different to that of the young, but because of the presence of co-morbidities, the elderly require a multi-disciplinary approach [30]. Because of ageing and alteration of the pharmacodynamics and pharmacokinetics, safe and effective treatment of heart failure in the elderly requires an understanding of clinical pharmacology of the drugs used. The ACC/AHA Guidelines Update [31] emphasised the important role of neurohormonal blockade by ACE inhibitors, ARBs, beta-adrenergic blockers and aldosterone antagonists, their roles in combined therapy and the selective addition of isosorbide nitrate and hydralazine [43].

Angiotensin-Converting Enzyme (ACE) Inhibitors

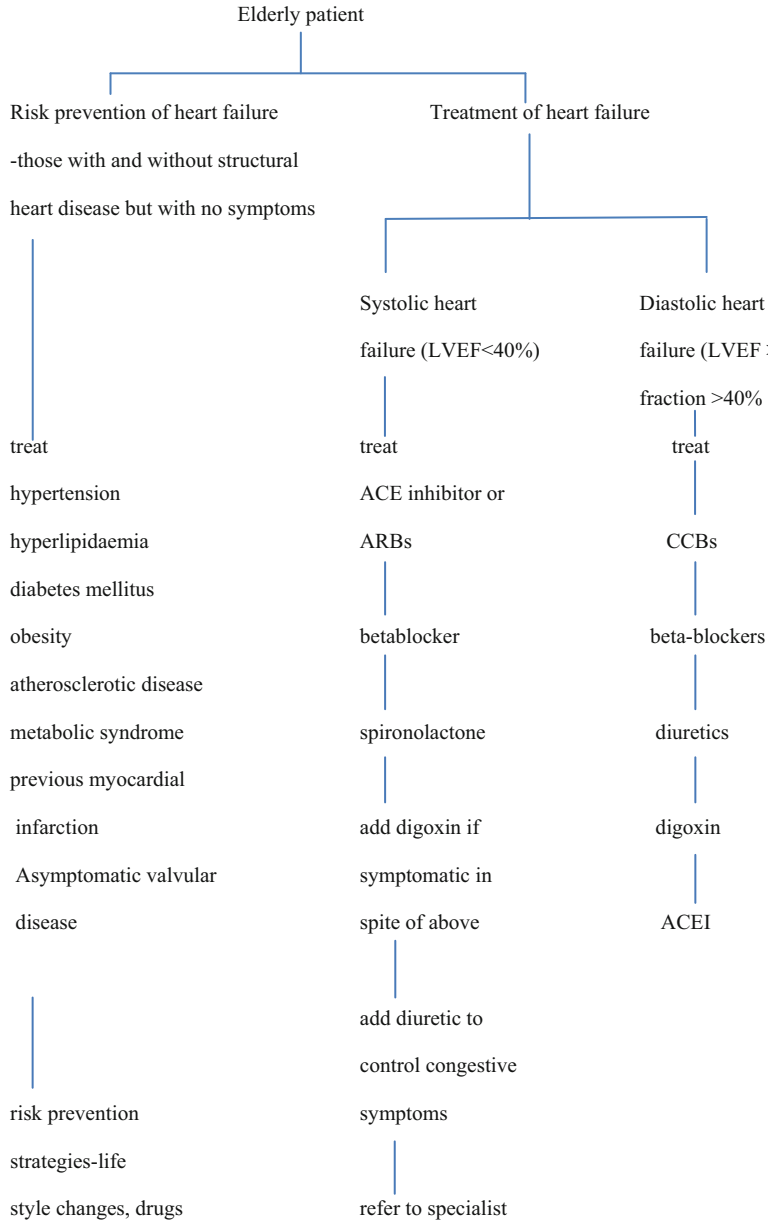
ACE inhibitors are efficient and important therapeutic agents for the treatment of cardiovascular disease in the elderly [44]. ACE inhibitors have been shown to improve survival in patients with heart failure due to systolic dysfunction, improve quality of life, increase exercise tolerance and reduce related hospitalisation [45, 46]. ACE inhibitors have good tolerability, and most drop-outs are due to side-effects such as cough (15%) [47], dizziness, hyperkalaemia, hypotension, altered taste and rarely angioedema (1 in 100) [47]. ACE inhibitors should be the initial baseline treatment in all patients with heart failure and systolic dysfunction unless there is a contraindication or inability to tolerate the drug. Normalisation of diastolic stiffness and regression in fibrous tissue may occur with ACE inhibition [48] with improvement in diastolic function [20].

ACE inhibitors may exacerbate renal insufficiency, and this is common in the elderly. Some rise in urea, creatinine and potassium is expected after commencing ACE inhibitor. The ACE inhibitors and angiotensin receptor blockers (ARBs) act on the kidney by reducing glomerular pressure which results in a decrease in eGFR and increase in the creatinine level. If the increase is small and asymptomatic, no action is necessary. First-dose hypotension may be minimised when initiating therapy in the elderly by smaller dose and control of such risk factors as pre-existing hypotension, excessive diuresis and low serum sodium levels. Patients with heart failure often have low blood pressure which limits the dose of ACE inhibitor or ARB prescribed. It is advisable to start on a low dose and the patient told to either sit or lie down for 2–4 h after the first dose and also to consider stopping diuretic for 24 h. The dose is doubled in two weekly intervals. The blood pressure, renal function and serum potassium should be checked before treatment, 1–2 weeks after starting at each dose increase until stable and then at least annually. The viable evidence is that there is no difference among the available ACE inhibitors. Absolute contraindications to their use are known bilateral renal artery stenosis and angioedema [47].

Angiotensin-Receptor Blockers (ARBs)

ARBs are comparable to ACE inhibitors in reducing mortality and hospitalisations. They do

Algorithm 1 Prevention and treatment of heart failure



cause cough less frequently and are reasonable alternatives to ACE inhibitors in those with cough or angioedema. There is a risk of hypotension, hyperkalaemia or renal dysfunction which is greater when combined with another ACE inhibitor or aldosterone antagonists. Many of the considerations are similar to ACE inhibitors. Patients with heart failure and with severe hypotension therefore cannot tolerate ARBs or ACE inhibitors and with significant worsening of renal function or hyperkalaemia have a very high mortality. The Candesartan in Heart Failure (CHARM) trials revealed that for patients intolerant to ACE inhibitors, the use of ARBs gave comparable benefits [49], but there was no benefit by the combination of both [50].

Beta-Blockers

Significant reduction in the mortality has been shown in patients with systolic heart failure who are on long-acting metoprolol or carvedilol and who are already taking ACE inhibitors [51, 52] unless there is a contraindication to their use. Potential complications are initial worsening heart failure, hypotension, bradycardia and heart block. Initiation and uptitration are best undertaken in consultation with a specialist. To minimise complications, start with an extremely small dose and increase gradually every 2 weeks, and if the small dose is tolerated, adjust the dose of other drugs such as diuretics while monitoring the heart rate, blood pressure and daily weight.

Aldosterone Antagonists

These are required for the long-term suppression of circulating levels of aldosterone. In diastolic dysfunction, there are increased levels of aldosterone due to activation of the renin-angiotensin-aldosterone system [20]. Excess of aldosterone is said to play a crucial role in altering normal cardiac tissue with fibrosis [20], and aldosterone antagonists inhibit this process. Spironolactone is the most widely used aldosterone antagonist and should be considered in selected patients with moderate to severe heart failure. It could cause life-threatening hyperkalaemia and the risk of which is increased with concomitant use of ACE inhibitors. Non-steroidal anti-inflammatory agents should be avoided, and potassium supplements should be ceased or reduced. Potassium levels and renal function should be monitored in 3 days following commencement and at 1 week and then monthly for at least the first 3 months. Gynaecomastia and other anti-androgen effects can occur. The initial dose should be small.

Newer more selective aldosterone blockers, for example, eplerenone, have lesser antiandrogenic and progestational effects than spironolactone thus enhancing tolerability [53]. Together with ACE inhibitors, loop diuretics and digoxin, the aldosterone blockers provide additional benefit in the treatment of heart failure [53].

Ivabradine

Ivabradine (Coralan) is a selective inhibitor of the hyperpolarisation-activated sodium channel If, [54] a mechanism different from beta-blockers and calcium channel blockers. It is an option for patients who are receiving optimal medical therapy for congestive heart failure and whose heart rate is more than 77 bpm, a left ventricular fraction less than 35% and New York Heart Association symptoms Class II or III [55, 56]. In elderly patients over the age of 75 years, addition of ivabradine to beta-blockers was beneficial in reducing heart rate, angina attacks and nitrate consumption in stable angina pectoris [57]. Adverse effects include bradycardia, first-degree heart block, dizziness and blurred vision [58].

Ionotropic Agents

Digoxin is used in heart failure and atrial fibrillation but has a limited second-line role in heart failure patients in sinus rhythm to relieve symptoms not controlled by diuretics, ACE inhibitors and beta-blockers. It is not intended as primary therapy and should be used with caution in elderly women [59]. The major side-effects are cardiac arrhythmias when administered in large doses, neurological manifestations such as confusion and visual disturbances and gastrointestinal symptoms (nausea and vomiting) and could have deleterious effect when used in the long term even when the digoxin levels are in the therapeutic range. The DIG study [60] revealed that digoxin was associated with significant decrease in hospitalisations and reduced the risk of worsening heart failure but had no significant effect on mortality in patients with systolic heart failure. The study further revealed that maximum benefit from digoxin was evident with lower serum digoxin concentrations (SDC)

(0.5–0.8 ng/ml) and a definite risk with higher SDC (>1.2 ng/ml) [61].

Vasodilators

The Vasodilator–Heart Failure Trial II (VHeFTII) has shown that the combination of hydralazine+ isosorbide reduced the mortality in heart failure patients [62]. This combination can be used together with ACE inhibitors or ARBs or as an alternative when the latter are contraindicated because of renal insufficiency. Table 1 shows the commonly used medication in heart failure.

Fluid and Electrolyte Abnormalities in Heart Failure

Fluid and electrolyte abnormalities are common in heart failure. This may be due to neurohumoral activation (stimulation of the renin-angiotensin-aldosterone system, sympatho-adrenergic stimulation) resulting from pathophysiological alterations in heart failure due to complications of therapy with diuretics, ACE inhibitors and cardiac glycosides [64]. Among the electrolyte abnormalities that occur in heart failure are disorders of potassium, sodium and magnesium. Hypokalaemia is treated with intake of foods rich in potassium or prescribing potassium supplements. In hyperkalaemia, potassium supplements are ceased, foods rich in potassium avoided, salt substitutes that contain potassium chloride avoided and the use of NSAIDs ceased or avoided. It may also be necessary to reduce or stop the ACE/ARB or aldosterone antagonist. In hyponatraemia, thiazide diuretics are ceased with reduction in fluid intake and medications which may cause reduction of sodium levels considered reducing.

Non-pharmacological Therapies

Implantable cardiac defibrillators are effective in terminating life-threatening ventricular tachyarrhythmias and preventing sudden death in systolic heart failure [59, 65]. Biventricular pacing studies have shown that resynchronisation therapy with biventricular pacing is of benefit in patients with severe and less severe symptoms from systolic heart failure and low left ventricular ejection fraction with broad QRS complexes especially of the LBBB pattern [53]. It is of benefit in patients with cardiomyopathy [66] and heart failure [67, 68].

Impact of Heart Failure

Heart failure in the elderly is a major public health problem [69] with the overall incidence and prevalence rising [70]. The impact of heart failure will significantly increase with the population ageing [71] and poses a heavy burden on the healthcare system [70]. Apart from physical functioning, other aspects such as emotional, economic burden, frequent hospitalisation and poor prognosis affect the QoL [70]. The physical health burden in patients with heart failure was found to be significantly greater than that seen in common chronic disorders [72]. Many with CHF report distressing symptoms, for example, depression and anxiety [73], which are associated with decreased HR-QoL [74].

There has not been any change in the outcomes, and this may largely be due to co-morbidities and frailty [69]. The survival of patients with HF-PEF has shown no changes [14]. In the United States, there are 5.7 million individual with heart failure [13], and by 2030 more than 8 million will have heart failure [72], and this is in part due to improvement in life expectancy and in survival of patients with ischaemic heart disease [14]. Patients with very advanced age with heart failure have fewer predictive factors of mortality, and they are functional deterioration, kidney disease, respiratory problems and hyponatraemia [75]. The direct costs of heart failure in the United States are projected to increase from $21 billion to $53 billion [72]. Heart failure patients expend more health resources through frequent hospitalisations, more ICU admissions, physicians' visits and longer stay in hospital [76]. Those in refractory heart failure will require psychosocial and spiritual support especially towards the end of life [77] (Box 3).

Table 1 Commonly used medication in heart failure

Drug	Initial daily dose	Maximum dose (s)	Clinical use
ACE inhibitors			
Captopril	6.25 mg tids	50 mg tds	Beneficial in HF regardless of severity and in patients with and without coronary heart disease
Enalapril	2.5 mg bd	10–20 mg bd	
Fosinopril	5–10 mg daily	40 mg daily	
Lisinopril	2.5–5 mg daily	20–40 mg daily	Initial baseline treatment in systolic heart failure
Perindopril	2 mg daily	8–16 mg daily	
Quinapril	5 mg daily	20 mg daily	
Ramipril	1.25–2.5 mg daily	10 mg daily	
Trandolapril	1 mg daily	4 mg daily	
Angiotensin receptor blockers			
Candesartan	4–8 mg daily	32 mg daily	Comparable and adequate to ACE inhibitors. No cough
Losartan	25–50 mg daily	50–100 mg daily	
Beta-blockers			
Metoprolol	12.5–25 mg daily	200 mg daily	In moderate to severe HF in patient (extended release) therapy
Carvedilol	3.125 mg bd	25 mg bd	Metoprolol useful when there is concomitant tachyarrhythmias following myocardial infarction
Bisoprolol	1.25 daily	10 mg daily	
If channel inhibitor			
Ivabradine	5 mg bd	7.5 mg bd	Congestive heart failure, stable angina
Aldosterone antagonists			
Spironolactone	12.5–25 mg daily	25 mg daily or bd	In severe HF, reduces mortality; monitored for hyperkalaemia
Eplerenone	25 mg daily	50 mg daily	
Vasodilators			
Hydralazine			Beneficial use limited by poor tolerability
Isosorbide nitrate			
Inotropic agents			
Digoxin	0.125 mg daily	0.125–0.25 mg daily	Is an option

Source of information: ACC/AHA 2005 [63] and GuideUpdate [31]

Box 3 Key Points: Heart Failure

Older patients could present with confusion, sleeplessness, agitation, depression, loss of appetite or nausea, with weakness, cough and breathlessness on exertion.

It is important to identify any precipitant cause of heart failure such as infection, anaemia, fever, pneumonia, thyrotoxicosis [8] or excessive salt intake and/or excessive alcohol intake and certain non-steroidal anti-inflammatory drugs such as indomethacin and ibuprofen.

The case for heart failure prevention is very strong. The Australian National Vascular Disease Prevention Alliance (NVDPA) in its guidelines categorises absolute risk as low, intermediate or high [32].

(*continued*)

Box 3 Key Points: Heart Failure (continued)

Prevention of heart failure should be on their list of all practitioners to act upon.

Multiple Choice Questions

1. The following in relation to heart failure in the elderly are true, EXCEPT:
   A. Heart failure is a major cause of disability in the elderly, and increasing age itself is a risk factor in its development.
   B. Approximately 80% of the hospitalised heart failure patients are in the 65-year or more age group.
   C. In most patients with heart failure, abnormalities of both systolic and diastolic dysfunction coexist.
   D. Patients with systolic heart failure have a lower death rate than patients with heart failure with preserved ejection fraction.
2. The following in relation to heart failure is true, EXCEPT.
   A. In 40% of patients presenting with dyspnoea, there was difficulty in distinguishing dyspnoea due to cardiac failure and dyspnoea due to other causes.
   B. The specific sign of heart failure in older patients is crackles in the lungs.
   C. B-type natriuretic peptide (BNP) is a useful tool in the diagnosis of heart failure.
   D. BNP levels are also affected in chronic obstructive airways disease and renal failure.
3. The following are true in heart failure, EXCEPT:
   A. In the elderly there is a shift from coronary heart disease to hypertension as the most common aetiology in the development of heart failure.
   B. In heart failure with preserved ejection fraction (HF-PEF), there is impaired relaxation and reduced compliance of the myocardium.
   C. In individuals with heart failure and left ejection fraction, more than 40% have systolic heart failure.
   D. Certain non-steroidal anti-inflammatory drugs such as ibuprofen and indomethacin can precipitate heart failure.
4. The following are true in the treatment of heart failure, EXCEPT:
   A. Patients with heart failure with preserved ejection fraction (HF-PEF) are very sensitive to diuretic.
   B. Among the electrolyte abnormalities that occur in heart failure are disorders of potassium, sodium and magnesium.
   C. ACE inhibitors may exacerbate renal insufficiency and this is common in the elderly.
   D. ACE inhibitors have been shown to worsen survival in patients with heart failure due to systolic dysfunction.
5. The following are true of ACE inhibitors EXCEPT:
   A. Patients with heart failure often have low blood pressure which limits the use of ACE inhibitors and ARBs.
   B. Significant reduction in the mortality has been shown in patients on metoprolol or carvedilol who are already taking ACE inhibitors.
   C. ACE inhibitors can be used in patients with renal artery stenosis and angioedema.
   D. Most drop-outs with ACE inhibitors are due to side-effects such as cough, hyperkalaemia, dizziness and altered taste.

MCQ Answers

1 = D; 2 = B; 3 = C; 4 = D; 5 = C

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Cardiac Arrhythmias

2

Contents

Abstract

Cardiac arrhythmias are a large concern among the elderly with increasing prevalence. Atrial premature contractions increase with age and were seen in up to 95% of older healthy volunteers at rest and during exercise in the absence of detectable cardiac disease. About 40% of the people who die from cardiovascular disease suffer from arrhythmias. Atrial fibrillation is common in the elderly, and the incidence and prevalence increase with age, with a prevalence of 8% in people 80 years and over. Drug therapy has a key role in the treatment of arrhythmias especially in long-term therapy. There are an array of procedures and devices for non-pharmacological treatment of arrhythmias. In elderly patients with AF, there is an increased risk of heart failure and embolic events which have a negative effect on the QoL and mental function. The present review will highlight the improvement that has occurred in clinical care.

Keywords

Cardiac arrhythmias · Atrial fibrillation · Multiform ventricular ectopy · Drug therapy · Procedures and devices for non-pharmacological treatment

Introduction

Cardiac arrhythmias are a large concern among the elderly with increasing prevalence [1, 2], and they occur so frequently that they are often

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_2

regarded as 'normal' and inevitable part of the ageing process [3]. Healthy population of the elderly show a substantial prevalence of supraventricular ectopic beats and ventricular ectopic beats both isolated and complex [4]. Atrial premature contractions increase with age and were seen in up to 95% of older healthy volunteers at rest and during exercise in the absence of detectable cardiac disease [5]. Likewise multiform ventricular ectopy had been reported in 80–90% of older men and women without detectable cardiac disease [5, 6]. About 40% of the people who die from cardiovascular disease suffer from arrhythmias [7].

Clinical Manifestations

Bradyarrhythmias

Sick Sinus Syndrome

Sick sinus syndrome or sinus node dysfunction includes (i) persistent sinus bradycardia, (ii) complete sino-atrial (SA) block, (iii) sinus arrest, (iv) SA block manifesting as SA Wenckebach and (v) bradycardia–tachycardia syndrome. It can be caused by drugs such as digoxin, calcium channel blockers and conditions like hypothyroidism or may be due to fibrous replacement of the sinus node. In most instances, the mere presence of a bradycardia without symptoms does not justify any intervention [8]. If symptomatic or does not resolve following alleviation of the condition that is causing it, then the treatment with a pacemaker is justified [8].

Atrioventricular Block

Conduction blocks can occur at the AV node, bundle of His or bundle branches. There are three categories of blocks, namely, AV block, bundle branch block and hemiblock.

First-degree atrioventricular heart block/PR interval is >0.2 s, and every P wave is followed by a QRS complex (in acute rheumatic fever, sarcoid heart disease and digitalis effect).

Second-degree atrioventricular heart block:

(a) Mobitz type I (Wenckebach block) progressive lengthening of PR interval until a P wave is blocked. PR interval after blocked beat is shorter than preceding conducted PR interval

(b) Mobitz type II: PR interval remains constant. Intermittently blocked P waves

(c) Second-degree high-grade atrioventricular block: A mathematical relationship between P and QRS complex has a conduction ratio of 3:1 or more.

Third-degree atrioventricular block

Impulses originating from the SA node cannot enter the ventricles when there is an AV block. This type of block can occur at the AV node, at the common bundle of His, or when both bundles are blocked. When this occurs, a new pacemaker distal to the block takes over, and this secondary pacemaker generally has an intrinsic rate of 30–50 impulses/minute which is slower than the SA node. There will be a dissociation of atrial and ventricular activity. Atrial rate is faster than the ventricular rate whether junctional or ventricular in origin. The QRS complex is usually wide.

Complete heart block may lead to syncopal (Stokes-Adams) attacks. It may be caused by digitalis toxicity, ischaemic heart disease, congenital heart disease, sclerodegenerative disease of the conductive tissue (Lenegr disease) and fibrocalceous involvement of the conductive tissue as well as the fibrous skeleton of the heart (Lev' disease) [9], and it is believed that the latter may be a variation of the normal ageing process [10].

Bundle branch block. When either the left or right bundle branch is blocked (bundle branch block), the impulses will travel from the atria to the ventricles, and the ventricles will still be driven by the SA node. However, the sequence and timing of the ventricular depolarization will be altered. A hemiblock occurs when left anterior or posterior fascicle of the left bundle branch is blocked.

Tachyarrhythmias

There are two types of fast heart rates: tachycardia where the rate is higher than 100 beats per minute and fibrillation where the rate is higher than

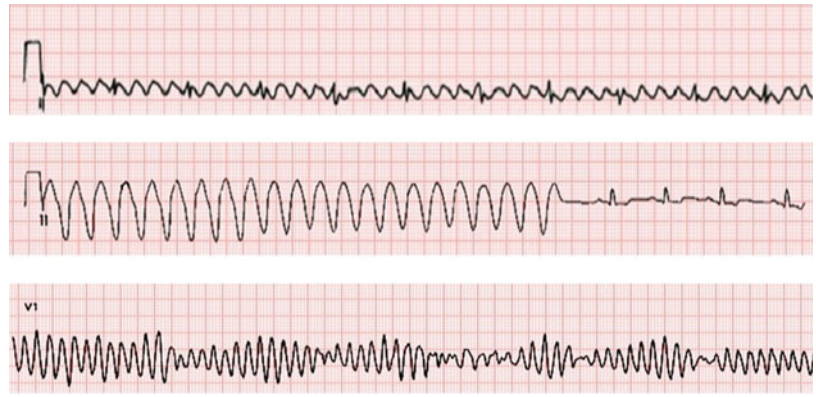

Fig. 1 Tachyarrhythmias – (i) atrial flutter, (ii) ventricular fibrillation, (iii) Torsades de pointes

350 beats per minute. The fast heart rates are categorized based on where they originate, namely, (i) in the upper chamber, atrial, and (ii) in the lower chamber, ventricles.

The fast rates that occur in the upper chamber are:

(i) Atrial flutter which is a rapid regular atrial rhythm at a rate of 200–300 beats per minute due to large re-entrant circuit that involves the lower lateral right atrium. The P waves show a saw-toothed appearance (Fig. 1).
(ii) Atrial fibrillation which is an irregular atrial rhythm at a rate of 300–600 beats per minute due to multiple interlacing wavelets of re-entrant activities. There are no well-defined P waves.
(iii) Supraventricular tachycardias or the preferred term is narrow QRS tachycardias because these arrhythmias may involve the ventricular tissue as well. AV node re-entrant tachycardia can occur in the elderly, less commonly supraventricular tachycardia due to accessory pathways (WPW syndrome). In this rhythm, tachycardia circuit will utilize atria, AV node, accessory pathways and ventricles.
(iv) Multifocal atrial tachycardia with atrial rates of 100–130 beats per minute with variation in the P wave morphology on the electrocardiogram [11].

The fast rates that occur in the lower chamber ventricles are ventricular tachycardia (VT), ventricular fibrillation (VF) and ventricular ectopy (ventricular premature beats). Ventricular tachycardia is a regular ventricular arrhythmia with ventricular rate up to 300 bpm. The two subgroups of ventricular tachycardia are (i) monophasic with typically regular rhythm, QRS identical in all the beats, and (ii) polymorphic with irregular rhythm and variation in the QRS complexes beat to beat. The ventricular tachycardias are characterized by a wide QRS complex and abnormal T waves. VTs have also been typified as (i) sustained VT, a fast VT that ceases after 30 s or with treatment, and (ii) non-sustained VT, a fast VT that ceases within 30 s (See Fig. 1).

Ventricular fibrillation is a rapid usually more than 300 bpm grossly irregular ventricular rhythm with marked variability in QRS cycle length, morphology and amplitude. Symptoms associated with ventricular arryhthmias are faintness, dizziness, blackouts, unconsciousness and cardiac arrest.

Torsades de pointes is characterized by a form of VT with a long QT or QTc and on the electrocardiogam by twisting of the peaks of the QRS complexes around the isoelectric line (see Fig. 1).

Treatment and Management of Cardiac Arrhythmias

Pharmacological

Drug therapy has a key role in the treatment of arrhythmias especially in long-term therapy [12]. Because of the narrow toxic–therapeutic relationship of antiarrhythmic agents, an understanding of the pharmacokinetics is vital [13]. Antiarrhythmic drugs had been categorized according to Vaughan

Williams classification whether their blocking action is predominantly the sodium, potassium or calcium channel or by blocking the beta-adrenergic receptors. There are four classes. Digoxin and adenosine had no place in the Vaughan Williams classification system, but this has been rectified by inclusion of class 5. Class 1 is subclassified as 1A, 1B and 1C. Class 1 are sodium channel blockers that reduce conduction velocity and thereby abolish tachyarrhythmias caused by re-entry circuits [14]. In the elderly, the risk associated with antiarrhythmic drugs especially class 1 is elevated [15]. Flecainide (class 1C) is useful for ventricular and supraventricular arrhythmias but is contraindicated in the presence of structural heart disease [11]. Class 2 inhibit the effect of adrenergic stimulation by blocking beta-adrenoceptors, and the beta-blockers mitigate sympathetic nervous system stimulation on the heart [11]. Class 3 typically block the potassium channels and by prolonging the refractory period abolish re-entry tachycardias [14]. Amiodarone is used in atrial fibrillation, atrial flutter and life-threatening arrhythmias refractory to other drugs [15] and in selected patients after implantation of cardioverter defibrillators [11, 16]. It is the most toxic antiarrhythmic agent and should be used only when other drugs have not been effective or tolerated [17]. Thyroid function should be tested every 6 months. Dronedarone is an amiodarone analogue which has been shown to be efficient in rhythm and rate control without any serious side effects in patients with AF [18]. The DIONYSOS study demonstrated better safety with dronedarone compared to amiodarone but lower efficacy in maintaining sinus rhythm in patients with AF (DIONYSOS study). Sotalol is well tolerated but can cause torsades de pointes [11]. Class 4 block the slow inward calcium channels, reduce pacemaker firing rate and reduce conduction velocity at the AV node [14]. Drugs such as verapamil and diltiazem are useful in slowing the ventricular rate in supraventricular tachycardia and slowing the ventricular rate of atrial flutter and atrial fibrillation [11]. Adenosine (class 5) is used in the acute management of supraventricular tachycardia and digoxin to control the ventricular rate in atrial fibrillation. In the elderly antiarrhythmic drugs frequently cause adverse effects; for instance, flecainide and amiodarone raised concerns, and attention was drawn to dronedarone, beta-blockers, calcium channel blockers and digitalis [19].

Non-pharmacological

There are an array of procedures and devices for non-pharmacological treatment of arrhythmias. The interventional therapies include permanent pacing for bradyarrhythmias, conventional antiarrhythmic surgery, percutaneous catheter ablation and implantable devices for bradyarrhythmias and tachyarrhythmias. In a survey, it was shown that in the elderly with indications of pacemaker implantation there was no limit of age [19].

Cardiac ablation offers a safe curative therapy for patients with recurrent SVTs and VTs. Arrhythmogenic foci located close to the pulmonary veins, sinus node, ventricular outflow tracts and microaortic commissure can be successfully ablated, and they can be precisely characterized by analysis of ECG patterns [20]. In haemodynamically stable ventricular tachycardias occurring in post-myocardial infarction, radiofrequency ablation is only moderately effective but may be an option in drug refractory patients [21]. In recurrent mechanisms of the arrhythmias where the impulse circulates in a loop, the loop can be outlined by creating a 3D electroanatomical map. The loop can be identified as in the case of atrioventricular nodal re-entrant tachycardia, atrial flutter or bundle branch ventricular tachycardia [20]. Implantable cardioverter defibrillator (ICD) has proved effective in conversion of life-threatening tachyarrhythmias and preventing sudden death in high-risk subjects. Management of the VT is management of the underlying disease. There are two treatment options for most patients: radiofrequency catheter ablation and implantable cardioverter defibrillator.

Atrial Fibrillation

Atrial fibrillation (AF) is an abnormal irregular rapid rhythm from the atria. The causes are inefficient contraction of the atria and is often accompanied by rapid ventricular rate. Atrial fibrillation (AF) is a relatively common arrhythmia. It is common in the elderly [18], and the incidence and

prevalence increase with age, with a prevalence of 8% in people 80 years and over [3]. It is more frequent in men than in women. It had been proposed that AF is produced by multiple wavelets of re-entrant activity. In paroxysmal AF, the rhythm abnormality often starts inside the pulmonary veins and spreads to involve the atria. In AF although the atria are stimulated giving rise to 300–600 beats per minute, the AV node cannot conduct all the impulses usually and can only allow about 170 impulses/minute to get through but irregularly.

Non-valvular atrial fibrillation (NVAF) increases the risk of stroke by about six times [22, 23]. Patients with AF are at increased risk of stroke, and in patients with NVAF, the risk of ischaemic stroke averages 5% per year, about three to five times that of people in sinus rhythm [22]. Those ageing 75 years or over or with specific risk factors have the highest risk for stroke [24]. AF affects 10% of the elderly over the age of 80 years. The annual risk for stroke increases with age, from 11.5% in ages 51–59 to 23% aged 80–89 years [25]. In the United States, there are more than two million adults with NVAF, and about 36% of patients between the ages 80 and 89 years have stroke and was attributed to NVAF [22]. Oral anticoagulation is required in patients with NVAF who have specific risk factors for stroke such as age, previous TIA/stroke, hypertension, diabetes mellitus, heart failure and coronary artery disease. More recently the Atherosclerosis Risk in Communities (ARIIC) study indicated that premature ventricular complexes (PVCs) were associated with new onset of atrial fibrillation and death [26], and an association between PVCs and stroke has been reported earlier. PVCs detected on a rhythm strip may be a newly identified marker [27] if not a risk factor for stroke.

Risk Factors and Causes

Risk factors in AF include age, male gender, hypertension, valvular heart disease and coronary artery disease among others, the last three being the most common predisposing conditions in the elderly. Obesity and sleep apnoea have been found to increase the risk of AF significantly. The causes of AF are shown in Box 1 and can be divided into cardiovascular and noncardiovascular. Among the heart disease that increases the incidence of AF are the valvular heart diseases especially mitral stenosis, mitral incompetence and tricuspid incompetence. About 70% of the patients with rheumatic heart disease develop AF. AF in myocardial infarction may be brief but may become persistent. About a quarter of the older patients with thyrotoxicosis develop AF. Binge drinkers can develop AF though usually transient. Medications such as theophylline can give rise to AF and so does caffeine.

Box 1 Causes of Atrial Fibrillation

Cardiovascular
- Long-standing hypertension
- Valvular heart disease
- Ischaemic heart disease
- Cardiomyopathies
- Infiltrative disease (e.g., haemochromatosis, amyloidosis, endomyocardial fibrosis)
- Atrial septal defect
- Pericarditis
- Sick sinus syndrome

Non-cardiovascular
- Hyperthyroidism
- Pheochromocytoma
- Hypokalaemia
- Hypomagnesemia
- Hypocalcaemia
- Drugs, alcohol, caffeine
- Pulmonary embolism
- Idiopathic ‘lone’ AF

Other causes include cardiac surgery, general surgery, sleep apnoea, subarachnoid haemorrhage, major ischaemic stroke and pneumonia.

Management

The most common causes are ischaemic heart disease, hypertension, valvular heart disease and hyperthyroidism. In the clinical evaluation of a patient with AF, the minimal requirements are

the history, physical examination, electrocardiogram, echocardiography and tests of thyroid and liver functions. The diagnosis of AF requires confirmation by electrocardiogram and in some instances telemetry or ambulatory Holter recordings.

The aim of treatment of AF is threefold: firstly, the recognition of causal and other associated factors; secondly, the decision as to rate control or correction of the rhythm disturbance; and thirdly, the prevention of thromboembolism. A number of classifications have been proposed for atrial fibrillation, but present guidelines are based according to its temporal pattern on first detected episode, paroxysmal, persistent, permanent and recurrent [25, 28]. The mainstay of treatment is drug therapy which includes the control of ventricular rate and the restoration and maintenance of sinus rhythm [29]. In terms of mortality, there is no significant difference between rhythm and rate control [18] . Rate control strategies have shown greater safety and lower costs of hospitalization, but some patients require rhythm control [30].

The American College of Cardiology (ACC), American Heart Association (AHAA) and the European Society of Cardiology (ESC) recommended the following classification based on clinical relevance and simplicity: first detected-only one diagnosed episode, paroxysmal–recurrent episodes that stop on their own in less than 7 days, persistent–recurrent episodes that last for more than 7 days and permanent–ongoing long-term episodes [31]. The first detected AF episode can be *paroxysmal* or *persistent*. The former treatment may not be necessary unless symptomatic, but need for anticoagulation should be evaluated. In the persistent AF, one could elect to rate control or could consider addition of antiarrhythmic drug therapy and cardioversion.

Chronic AF can be *paroxysmal* or *sustained form (persistent* or *permanent*) [32]. Patients with *paroxysmal* AF have episodes of varying duration and may revert spontaneously to sinus rhythm. For those with minimal or no symptoms, anticoagulation with rate control may suffice. Patients with disabling symptoms besides anticoagulation and rate control with antiarrhythmic drug therapy may ablation if this fails [25].

With *persistent* AF, spontaneous conversion is much less likely, and conversion to sinus rhythm is either by electrical cardioversion or medications. The former is associated with serious side effects more so in the very elderly. Those with minimal or no symptoms require anticoagulation and rate control. The results of the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) trial [33] revealed that in the elderly asymptomatic population of patients with AF with risk factors for stroke or death, rate control is at least as good as rhythm control [34]. In most elderly patients with sustained AF, rate control should be the preferred approach [32]. If there are disabling symptoms, antiarrhythmic drugs are included, and electrical cardioversion as needed. In the elderly, the choice of antiarrhythmic drugs is limited. Amiodarone and flecainide are used for medical cardioversion; the latter however is contraindicated with structural heart disease. Amiodarone is effective in maintaining sinus rhythm after cardioversion in patients with AF. Its long-term use can cause thyroid dysfunction, heapatotoxicity and other extracardiac side effects [30]. Other drugs used are propafenone and ibutilide. The disadvantages of the conventional agents are the side effects and, with long-term use, the possibility of life-threatening adverse effects including drug toxicity and pro-arrythmia [18]. Furthermore they differ in their efficacy in maintaining sinus rhythm after cardioversion with potential drug interactions and tolerability problems [30]. A new class 3 antiarrhythmic dronedarone, an amiodarone analogue, has been shown to be efficient in controlling rate and rhythm. When compared to amiodarone, it is less effective and has a better safety profile [18, 30]. Unlike amiodarone, dronedarone was shown to have no thyroid toxicity and was reported by the ATHENA investigators [35, 36] to reduce the incidence of hospitalization from cardiovascular event, but the follow-up lasted for only a year.

Patients with *permanent* AF are patients in whom cardioversion has failed or not attempted, and cardioversion is not an option to restore sinus rhythm [37]. Management of these patients typically includes anticoagulation and rate control

[37]. In patients treated with rate control, the medications are used to slow the conduction of the AV node thereby slowing the ventricular rate, and the drugs used are beta-blocker, calcium channel blocker and digoxin. Beta-blockers are the most effective agents for monotherapy followed by the rate-limiting calcium antagonists like verapamil and diltiazem [38], as these drugs control both exertional and resting heart rate. Digoxin however does not control exertional rate, and furthermore the efficacy of digoxin in controlling AF ventricular rate is also limited during paroxysms of AF and is associated with longer attacks [39], and hence it is no longer the drug of first choice for rate control. Continued anticoagulation is mandatory. The disadvantages here are the difficulty to control the rate at times to relieve symptoms and the risks associated with anticoagulation.

Non-pharmacological strategies include radiofrequency catheter ablation, use of pacemaker or implantable atrial defibrillator and several surgical treatments. In the elderly patients, most centres adopt a cautious attitude to AF ablation [19]. With radiofrequency ablation, the success rates are variable and could approximate 75%, but this may require multiple procedures [40], and in patients with permanent AF, the risk of complications is higher [41]. Patients with paroxysmal AF with structural heart disease and smaller atria are most likely to benefit from catheter ablation [42]. In elderly patients, most centres adopt a cautious approach to AF ablation but again, most centres regard that age would not have an effect on the success rate of ablation [43]. The MAZE requires cardiac surgery, but it is effective in preventing arrhythmia recurrence. Cryomaze procedure using an argon-powered cold probe creates electrical barriers in the upper chamber of the heart blocking the electrical activity permanently. At present ablation and surgical therapies for atrial fibrillation are mainly symptom control. There are ongoing studies to see whether these therapies would have favourable effect on thromboembolic complications and mortality. When adequate rate control has not been achieved by pharmacological means, permanent pacemaker implantation followed by AF nodal ablation may be an alternate approach.

CHADS score or CHADS2 score is one method of determining the risk of stroke in patients with AF in primary prevention and as a basis to determine the risk–benefit of anticoagulation therapy. The score distinguishes between patients with high risk and low risk of stroke [44, 45]. Many clinicians feel that age over 75 years is equally a potent risk factor as a history of previous stroke. The European Society of Cardiology (ESC) has recognized this inequality of risk in the CHADS and had developed a more detailed risk assessment tool, the CHA2DS2-VASc score [46], which has now superseded the former. The CHA2DS2-VASc score has significantly improved the classification of AF patients at low and intermediate risk of stroke [47] and has helped to avoid unnecessary anticoagulation therapy [48]. A score of 2 or more is of moderate or high risk, and anticoagulation is recommended.

Patients with AF who are on medical prophylaxis are at high risk of bleeding complications, and it is important to evaluate the risk of bleeding. The European Society of Cardiology in its guidelines released the HAS-BLED score as a predictive tool to assess the bleeding risk [49]. The risk factors in the tool includes age 75 years and over, vascular disease and gender. A score of more than 3 indicates high risk [50].

Warfarin is recommended in high-risk patients to prevent thromboembolism unless the drug is contraindicated. Warfarin is more effective although aspirin is most commonly used as an alternative to warfarin. The addition of clopidogrel to aspirin reduces the risk of major vascular events by 11% particularly stroke but increases the risk of major haemorrhage by 57% [51]. According to the ACTIVE-W trial, warfarin was more effective than aspirin plus clopidogrel in preventing cerebrovascular events, and the danger of bleeding was similar [52].

There is no advantage for patients well controlled on warfarin to switch over to one of the newer anticoagulants. In selected patients, an anticoagulant with a direct thrombin inhibition, dabigatran, may be an alternative to vitamin K antagonists like warfarin. Other effective substitutes besides dabigatran for warfarin include factor Xa inhibitors such as apixaban, rivaroxaban

and edoxaban. Dabigatran has been shown to be equally effective as warfarin in stroke prevention in atrial fibrillation [53]. The randomised evaluation of long-term anticoagulation study (RE-LY study) studied patients with non-valvular AF and at least one risk factor of stroke. Two doses of dabigatran (110 mg twice daily or 150 mg twice daily) dose blinded to patients and the researchers were compared with open-label warfarin with target INR of 2–3 [52]. The 150 mg twice daily was superior to warfarin in reducing stroke and embolization efficacy with similar risk of bleeding although there was an increase of gastrointestinal bleeding with this dose and seemed to be predominantly in the age group 75 years and over. The lower dose of 110 mg twice daily showed similar efficacy with warfarin in reducing stroke and reduced rates of major bleeding. Both doses however showed a significant reduction of intracranial haemorrhage of about 70% compared with warfarin [54]. Rivaroxaban and apixapan have also been shown to be similarly effective [54]. The main advantage of the novel oral anticoagulants compared to warfarin is that no routine anticoagulation monitoring is required and involves fixed dosages [55]. The ROCKET AF [56] and the ARISTOTLE [57] trials have shown that the new oral anticoagulants are better than warfarin in relation to intracerebral haemorrhage and haemorrhagic stroke. Furthermore, single-dose regimen irrespective of age, gender and body weight should benefit most patients. However, in case of bleeding apart from dabigatran, there is no antidote available as yet. Although the new anticoagulants have equal if not better efficacy and an equal or better safety profile, they have not totally replaced the vitamin K antagonists [19]. The choice in selection will become more apparent when the new vitamin K antagonists become more widely used [58, 59].

More recently life-threatening haemorrhage have been reported in the elderly with poor renal function taking dabigatran [60, 61]. In the old age group due to age-related decline in the creatinine clearance, there is accumulation of dabigatran, and hence safe dosing in the elderly will depend on the creatinine clearance. These agents should be not used when the creatinine clearance is less than 30 ml/min/1.73 m^2. The Cockcroft-Gault formula is the most appropriate method to calculate the creatinine clearance [62]. Renal excretion accounts for 25% of apixaban clearance.

Impact of Arrhythmias on Quality of Life

As the population ages, there will be an increased prevalence of cardiac arrhythmia resulting in greater impact on healthcare resource utilization. In elderly patients with AF, there is an increased risk of heart failure and embolic events which have a negative effect on the QoL and mental function [63]. The most feared complication of AF is the AF-related stroke [63]. The Rotterdam study showed that both Alzheimer's disease and senility were more common in patients with AF [64, 65]. In a study of the relationship between QoL and perceived self-reported symptoms in an elderly with heart failure, the investigators found that QoL was notably worse in those patients with perceptions of severe arrhythmic episodes and in those with symptoms of exercise intolerance and dizziness [66]. Furthermore the study found that those with symptomatic heart failure experience poor QoL [66]. The Birmingham Atrial Fibrillation Treatment of the Aged Study found that there was little impact on generic QoL in patients with chronic AF in the absence of co-morbidities [67] (Box 2).

Box 2 Key Points. Arrhythmias

The aims in the management of AF are threefold: (1) the recognition of the causal and associated factors and their treatment, (2) the decision as to rate control or correction of the rhythm disturbance and (3) prevention of thromboemboli.

The CHA2DS2-VASc score in evaluating the risk of stroke in patients with AF has now superseded the CHADS and CHADS2 [46, 47].

The European Society of Cardiology in its guidelines released the HAS-BLED

(*continued*)

Box 2 Key Points. Arrhythmias (continued)
score, a predictive tool to assess the bleeding risk [49].

Warfarin is recommended in high-risk patients to prevent thromboembolism unless the drug is contraindicated.

There is no advantage for patients well who are controlled on warfarin to switch over to one of the new anticoagulants.

In selected patients, an anticoagulant with a direct thrombin inhibition or antifactor X action such as dabigatran, rivaroxaban and apixaban may be an alternative to vitamin K antagonists like warfarin.

More recently life-threatening haemorrhage have been reported in the elderly with poor renal function taking dabigatran [60, 61].

There is an array of procedures and devices for non-pharmacological treatment of arrhythmias. The interventional therapies include permanent pacing for bradyarrhythmia, conventional antiarrhythmic surgery, percutaneous catheter ablation and implantable devices for tachyarrhythmia.

Case Study of an Elderly Patient with Palpitations

Presentation

An 80-year-old man was seen in the emergency department with a 'pounding heart' and light-headedness of about an hour duration. He has had similar complaints on several occasions over the past 3–4 months. It comes on suddenly and lasts for variable period of time, from a few minutes to several hours, and ceases suddenly and usually brought on by physical effort. These episodes are not accompanied by chest pain or breathlessness. Three weeks earlier he had developed, he developed sudden weakness of his right arm and leg with numbness, and according to his wife, she could not understand what he was saying. The symptoms resolved within an hour. He was seen by his family physician and was prescribed aspirin. He is diabetic and is on metformin 500 mg twice daily, and the HbA1c done a few days ago was 7%. Examination of the cardiovascular system included a blood pressure of 110/70 mmHg. The pulse was 80/minute and irregular and the heart rate 116/minute. There were no audible carotid bruits. No other sounds were heard at the apex and there were no murmurs. The lungs were clear and the central nervous system was normal. An electrocardiogram confirmed atrial fibrillation and no other abnormality. Echocardiography showed normal left ventricular systolic function, normal left ventricle and atrium and no evidence of valvular disease. Carotid Dopplers were normal.

The diagnoses were atrial fibrillation (AF) and transient ischaemic attack (TIA).

Comment

Based on the patient's risk factors, the management of AF has three objectives: rate control [68], prevention of thromboembolism and correction of the rhythm [69]. The major complication of AF is stroke, and stroke increases with age. The drug options for controlling the heart rate are the beta-blockers, calcium channel blockers and digoxin to achieve a heart rate between 60 and 80 bpm at rest. As to whether a strict rate control at rest and with exercise is preferred to a lenient approach, recent studies have suggested that a lenient approach is acceptable. Several randomized trials have shown no mortality benefit between rate control and cardioversion. The European Atrial Fibrillation Trial (EAFT) has shown that anticoagulation was superior to aspirin for prevention of stroke in patients with AF and a recent TIA. Patients with a high risk of stroke $CHAD_2>2$ or $CHA_2DS_2>2$ requires long-term coagulation.

Multiple Choice Questions

1. The following regarding atrial fibrillation (AF) are true, *except*:
   A. Modifiable risk factors for AF are diabetes and hypertension.
   B. The age-specific prevalence of AF is higher in men then in women.
   C. The most frequent cause of cerebral embolism is AF.
   D. AF is decreasing in frequency with the control of cardiovascular risk factors.
2. The following changes in the electrocardiogram are correct, *except*:
   A. In a patient with tachycardia, a narrow QRS (120 ms) on the ECG indicates supraventricular tachycardia.
   B. An irregular pulse of 180/min is likely to be atrial fibrillation.
   C. Torsades de pointes is a rapid ventricular tachycardia that oscillates above and below the isoelectric line on ECG.
   D. In third-degree AV block, there is dissociation of atrial and ventricular activity – the atrial rate is slower than the ventricular rate.
3. In the management of cardiac arrhythmias, the following are true, *except*:
   A. Cardiac ablation offers a safe and corrective therapy for recurrent supraventricular tachycardias.
   B. Amiodarone may be used to prevent recurrent episodes of ventricular tachycardia.
   C. Implantable cardioventricular defibrillators (ICD) have not proved effective in conversion of life-threatening tachyarrhythmias preventing sudden death in high-risk subjects.
   D. The Cox-Maze III surgical protocol for prevention of AF has reduced the need for long-term anticoagulation.
4. The following patients with atrial fibrillation require anticoagulation with warfarin, *except*:
   A. Associated mitral stenosis.
   B. Associated with left ventricular failure.
   C. Atrial fibrillation lasting for less than 24 h.
   D. Past history of a cerebral thromboembolism.

MCQ Answers

1 = D; 2 = D; 3 = C; 4 = C

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Infective Endocarditis

3

Contents

Abstract

The epidemiology of infective endocarditis (IE) is changing for several reasons. The older patients are at a high risk of contracting IE due greatly to increased prevalence in patients with inbody cardiac devices. The microbiology of the disease has also changed from streptococcus to healthcare-associated staphylococcus. Recently, many studies have shown a trend towards increasing incidence of *Staphylococcus aureus* IE. IE in the elderly caused less severe symptoms than in the young. Non-specific generalized symptoms, myalgias, arthralgias, malaise, fatigue, loss of weight and sweats, are also common though rigours are much more common in acute IE. Embolism and immune-mediated phenomena are common in the elderly. The protean nature of IE requires a diagnostic strategy that will be sensitive for disease detection and specific for its exclusion across all forms of the disease. Successful outcome will depend on early diagnosis, effective treatment and timely recognition of complications. The mortality of prosthetic IE caused by *Staphylococcus aureus* treated medically is 75%, and in the case of medical plus surgical treatment, it is 25%.

Keywords

Infective endocarditis · Cardiac devices · Staphylococcus · Streptococcus · Embolism

Introduction

The epidemiology of infective endocarditis (IE) is changing for several reasons. The older patients are at a high risk of contracting IE [1, 2] due greatly to increased prevalence in patients with inbody cardiac devices [3]. The microbiology of the disease has also changed from streptococcus to healthcare-associated staphylococcus [4]. In the last decade, staphylococcus and enterococci

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_7

IE has increased, while culture-negative IE has decreased [2]. The increase of frequency of IE in older patients is due to an increase in the life expectancy and general ageing of the population, longer survival of patients with congenital and valvular disease of the heart, the use of intravenous catheters and prosthetic devices [5], proliferation of invasive procedures [6] and higher prevalence of hospital-acquired bacteraemia [7, 8]. The Euro Heart Survey on Valvular Heart Disease illustrated that 26% of the cases of infective endocarditis was in patients over 70 years [9]. A French study concluded that IE increased with increasing age, 31 cases/million population in patients over 50 which peaked to 145 cases/million between the ages of 70 and 80 [10].

Streptococcus spp. are the most common cause and account for 25–75% of endocarditis cases; *S. viridans* is less prevalent in older patients and *S. bovis*, a non-enterococcal group D streptococcus, in up to 25%. In approximately 80% of cases, the predominant organisms in the elderly population are streptococci and staphylococci [11]. *Staphylococcus aureus* has become the primary pathogen of endocarditis with the present-day use of intravascular devices [12], and elderly diabetic patients are at an increased risk of bacteraemia and IE [13]. Recently, many studies have shown a trend towards increasing incidence of *Staphylococcus aureus* IE [14, 15]. Enterococci can account for 25% in the elderly, and some studies have noted a high prevalence in the elderly [16]. Other commonly encountered organisms are the HACEK organisms (*Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species and *Kingella* species) [17] (Table 1).

The portal of entry and subsequent consequences of microbiology show specific features of IE in the elderly as compared with younger patients [9, 18]. Manipulations or procedures of oral cavity, genito-urinary tract (prostatic and vesical disease) and gastrointestinal tract (colonic lesions) commonly produce transient bacteraemia with streptococci and staphylococci in the elderly. Prosthetic valve endocarditis is more frequent [1, 16, 19] and accounts for 10–15% in most series [20]. In the elderly pacemaker endocarditis occurs most often with difficulties in diagnosis and causes a poor prognosis [9].

Table 1 Organisms encountered

Common	Uncommon
Streptococci	Coagulase-negative enterococci
	Staphylococci
Staphylococci	*Coxiella burnetii*
HACEK organisms	Brucellae
Haemophilus parainfluenzae	*Candida* and *Aspergillus*
Haemophilus aphrophilus	*Legionella*
Actinobacillus [*Haemophilus*]	*Pseudomonas*
Actinobacillus actinomycetemcomitans	
Cardiobacterium hominis	
Eikenella species	
Kingella species	

Source of information: Bayer et al. [17]

A variety of cardiac abnormalities predispose to IE. All valvular lesions are at risk of endocarditis. With advancing age there is increase in the degenerative valvular heart disease, increase in the prevalence of aortic stenosis with calcification and progressive calcification of the mitral annulus all of which increases the susceptibility to infective endocarditis in the elderly [11]. Likewise in the elderly, bicuspid aortic valve and mitral valve prolapse with mitral regurgitation are increasingly associated with infective endocarditis and overall in the elderly the mitral valve is somewhat more often affected [11].

Clinical Manifestations

The clinical presentation of acute IE is quite different from that of subacute disease. The symptoms and signs may be protean and to a large extent determined by the nature of the infecting organisms. The current data suggests that the clinical features are fairly similar across age groups [21]. Another study too found no difference in the clinical presentations between different age groups but a non-significant trend towards delayed diagnosis in the elderly [18]. Other

studies have found different clinical characteristics in different age groups [11]. IE in the elderly caused less severe symptoms than in the young [16]. Fever and cardiac symptoms are common, and in acute IE, the fever may be between 39.4 and 40.6°C and often remittent [21], whereas in subacute endocarditis, the fever is usually low grade, rarely exceeds 39.5 °C. In the elderly fever occurred less frequently [16, 22] and may be slight, or the patient may be afebrile [23]. Non-specific generalized symptoms, myalgias, arthralgias, malaise, fatigue, loss of weight and sweats, are also common though rigours are much more common in acute IE.

Cardiac murmurs occur in about 90% of the cases. The presence of a murmur reflects underlying congenital or valvular lesion. A new or changing murmur is heard in 36–52% of patients with IE, but these murmurs are heard less frequently in the elderly [24]. Changes in the intensity of the murmur may be associated with the development of anaemia, high fever or tachycardia and are often of little significance [21]. The appearance of a new murmur during the course of the illness is a diagnostic event, and failure to detect the same may delay in diagnosis [25]. A new aortic diastolic murmur suggests a rupture or fenestration of an aortic leaflet, or dilatation of the aortic annulus, and in the case of the mitral valve, a regurgitant murmur suggests rupture of the chordae tendineae or fenestration of the mitral valve leaflet [21] and may require surgery. Splenomegaly is seen more with subacute IE [22]. About half of the patients with IE have cutaneous manifestations, but these are becoming less common with early and effective therapy. The cutaneous or peripheral manifestations include clubbing, nail bed petechiae, splinter haemorrhages, Osler's nodes and Janeway's lesion. The latter two are uncommon [26]. Roth spots are seen in less than 5% [27]. The immunological vascular phenomena are more characteristic of subacute IE rather than acute IE, for the latter evolves too quickly for their occurrence [17] and usually results from left-sided valvular involvement [28]. Embolism and immune-mediated phenomena are common in the elderly [1]. Mitral valve vegetations, embolism and mortality were more common in older patients, and TV vegetations, IV drug use [29] and *S. aureus* endocarditis [25, 30] were more common in younger patients [31]. Box 1 shows the clinical manifestations of IE.

Box 1 Clinical Presentation of IE

Fever, fever of unknown origin
Cardiac murmur
Unexplained cardiac failure
Non-specific presentation (weakness, fatigue, anorexia, loss of weight)
Meningitis
Anaemia
Renal failure
Embolic phenomena (neurological, renal, splenic, pulmonary, etc., appear late)
Musculoskeletal (myalgia, arthralgia, arthritis, appear early)

Complications

The complications are shown in Box 2.

Box 2 Complications in IE

Congestive heart failure
Risk of embolization
Periannular extension
Splenic abscess
Mycotic aneurysm
Intracerebral mycotic aneurysms
Extra cerebral mycotic aneurysms

Information source: Bayer et al. [28]

Diagnosis

The protean nature of IE requires a diagnostic strategy that will be sensitive for disease detection and specific for its exclusion across all forms of the disease [28]. The major diagnostic criteria for IE are positive blood cultures and not only identify the organism but also its antimicrobial susceptibility [32, 33]. In less than 5% of patients

with IE, the blood cultures are negative. Then the diagnosis is made with strict diagnostic criteria [34]. Inability to isolate the organism may be due to (i) prior administration of antibiotic (ii), fastidious infection and (iii) inadequate laboratory techniques.

The Duke criteria, a diagnostic strategy, have a number of parameters with echocardiographic requirements [35]. It stratifies suspect patients into three categories: *definite* cases identified clinically or pathologically (unidentified by surgery or autopsy), *possible* cases falling short of definite IE, and *rejected* cases (no pathological evidence of IE at autopsy or surgery), a firm alternative diagnosis or rapid resolution of the clinical syndrome with either no treatment or short-term antibiotic therapy (Tables 1 and 2).

Duke criteria incorporate echocardiographic (ECHO) findings in the diagnostic strategy [35], and further modifications have been proposed [36]. ECHO plays an important role in the diagnosis and management of IE. It is a sensitive and accurate method of detecting valvular vegetations despite in some old people with valvular sclerosis, the focal thickenings on one or more valvular structures may be confused with vegetations. Some form of ECHO should be performed in all patients suspected of having IE. Transthoracic echocardiography (TTE) has a specificity of 98% [37] and sensitivity of 60% [37–39] for vegetations. It is inadequate in patients with chest wall deformities, obesity and chronic obstructive pulmonary disease [17]. Furthermore TTE by itself cannot exclude vegetations on prosthetic valves, periannular abscesses, leaflet perforation and fistulae [39, 40]. The high sensitivity of TEE promoted early diagnosis, [16, 18]. It also discriminates multiple vegetations, satellite lesions, fistulas, ring abscesses, location and extent of abscess cavities [41], valvular perforations [42] and aneurysms unlike TTE which only shows the vegetations [24]. However a negative TEE in a situation where the clinical suspicion is high it does not have the diagnostic accuracy to rule out.

Accuracy to rule out vegetation in IE and distinguishing true vegetations and other

Table 2 Antibiotic treatment of infective endocarditis

I. Streptococcus strains sensitive to penicillin (MIC <0.2 ug/ml). All streptococci must be evaluated for susceptibility to penicillin by determining the MIC
(i) Penicillin G 12-18MU IV 12 hourly for 4 weeks
(ii) Ceftriaxone 2 gm IV once daily for 4 weeks
(iii) Ceftriaxone 2 gm IV once daily for 2 weeks** plus
Gentamicin 1 mg/kg IV/IM every 8 h for 2 weeks**
**short-duration combination therapy for penicillin-susceptible streptococcus endocarditis although successful is not recommended for general use (Durack and Karchmer 2006)
(iv) Vancomycin 1 g IV every 12 h for 4 weeks *
*with penicillin allergy
Ib. Penicillin-resistant viridans and most strains of non-enterococcal streptococcus (MIC 0.2–5 ug/ml). Screening for high-level resistance to gentamicin
(i) Penicillin G 3MU IV every 4 h for 4 weeks plus
Gentamicin 1 mg/kg IV/IM every 8 h for 4 weeks
(ii) MIC >0.5 ug/ml. Treat with one of the standard regimes for enterococcal endocarditis
(iii) MIC > than 1.0 ug/ml. Vancomycin 1 g IV 12 hourly for 4 weeks
II. Enterococci becoming increasingly resistant not only to aminoglycosides but also to penicillin G and vancomycin. Causative strain must be screened for high-level resistance to gentamicin
(i) Single-drug therapy penicillin for 8 weeks, ampicillin for 8 weeks, vancomycin for 8 weeks
(ii) Penicillin G 3MU IV every 4 h for 6 weeks plus
Gentamicin 1 mg/kg IV/IM 8 hourly for 4–6 weeks
(iii) Vancomycin IV every 12 h for 6 weeks plus
Gentamicin 1 mg/kg UIV/IM 8 hourly for 6 weeks
III. *Staphylococcus*
(i) Methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-sensitive *Staphylococcus* epidermidis (MSSE)
Cloxacillin 2 g IV 4 hourly for <6 weeks plus
Gentamicin 1 mg/kg IV/IM 8 hourly for the first 2 weeks plus
Rifampicin 300 mg PO 8 hourly for <6 weeks
(ii) Methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus* epidermidis (MRSE)
Vancomycin 1 gm IV 12 hourly for 6 weeks plus gentamicin mg/kg IV/IM 8 hourly
IV. HACEK group (*Haemophilus aphrophilus*, *Haemophilus parainfluenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium*, *Eikenella* species *and Kingella* species)

(*continued*)

Table 2 (continued)

(i) Ceftriaxone 2 mg IM/IV daily for 4 weeks
(ii) Ampicillin – sulbactam 2 g IV 4 hourly for 4 weeks plus
Gentamicin 1 mg/kg IV/IM 8 hourly for 4 weeks

Sources of information: Durack and Karchmer [21], Dhawan [11] and Wilson et al. [44]

IE-related changes such as ruptured chordae. When both TEE and TTE studies are negative, there is a 95% negative predictive value [28, 43]. A repeat TEE study is warranted in 7–10 days if there is high clinical suspicion of IE. TEE is also useful where imaging is difficult such as those with prosthetic valves or poor transthoracic windows or patients on mechanical ventilators [24] (Box 3).

Box 3 Diagnosis

I. Blood cultures (a negative blood culture seen in <5% of endocarditis)
II. ECHO and Doppler ultrasonography
    TTE overall 80%
    TEE
III. Laboratory analysis
    Anaemia (70–90% of cases)
    ESR (90–100%)
    Urinalysis
        Proteinuria (50–65%)
    Rheumatoid factor in 50%

Management and Treatment of Infective Endocarditis

Successful outcome will depend on early diagnosis, effective treatment and timely recognition of complications. Effective treatment requires identification of the causative organism and establishing the antimicrobial susceptibility. Empirical therapy with bactericidal antibiotics should be started immediately after blood samples are taken for culture. In the subacute IE, the therapy is directed at streptococci. Table 2 shows the antibiotic treatment of infective endocarditis.

About 30% of patients with infective endocarditis will need surgery in the early phase of the infection [45]. The indications for surgical intervention in IE are heart failure, large and/or mobile vegetations and embolic episode, perivalvular infection, unfavourable fever and inflammatory syndrome, fungal infection, difficulty to treat microorganisms [46], neurological complications [47, 48], unstable prosthesis and prosthetic infective endocarditis [49].

Impact

Patients with IE are getting older [2]. In the elderly due to the insidious presentation, IE is more difficult to diagnose leading to delayed treatment [9]. The prognosis is poor in the elderly with IE, and in one study, the hospital mortality was 17% in patients over 70 and 7% below the age of 50 years [11]. Another study showed a higher in-hospital mortality of 24.9%, and age was an independent predictor of mortality in patients older than 65 years [1]. Several studies have demonstrated that in IE in the elderly, there is a limited use of surgical treatment with higher mortality [1, 16, 19]. The mortality of prosthetic IE caused by *Staphylococcus aureus* treated medically is 75%, and in the case of medical plus surgical treatment, it is 25% [49] (Box 4).

Box 4 Key Points: Infective Endocarditis

The older patients are at high risk of contracting IE [1, 2] due to the increased prevalence in patients with inbody cardiac devices [3].

The microbiology of the disease has also changed from streptococcus to healthcare-associated staphylococcus [4].

In the last decade, staphylococcus and enterococci IE had increased, culture-negative IE has decreased and enterococci IE has increased [2].

(*continued*)

Box 4 Key Points: Infective Endocarditis (continued)

A new or changing murmur is heard in 36–52% of patients with IE, but these murmurs are heard less frequently in the elderly [24].

The protean nature of IE requires a diagnostic strategy that will be sensitive for disease detection and specific for its exclusion across all forms of the disease [17].

The major diagnostic criteria for IE are positive blood cultures and not only identify the organism but also its antimicrobial susceptibility [32, 33].

The high sensitivity of TEE promotes early diagnosis [16].

TEE also discriminates multiple vegetations, satellite lesions, fistulas, ring abscesses, valvular perforations and aneurysms unlike TTE which only shows the vegetations [24].

Successful outcome will depend on early diagnosis, effective treatment and timely recognition of complications.

Multiple Choice Questions

1. The following are true relating to infective endocarditis (IE), *except*:
   A. Presently *Staphylococcus aureus* is the primary pathogen causing IE.
   B. Transient bacteraemia is commonly produced by manipulations or procedures of oral cavity, gastrointestinal tract and genito-urinary tract.
   C. A new or changing murmur is heard in 30–52% of patients with IE, but the murmurs are heard much more frequently in the elderly.
   D. In the elderly non-specific symptoms may lead to incorrect diagnosis.
2. In establishing a diagnosis of infective endocarditis (IE), the following are true, *except*:
   A. Negative blood cultures seen in one-third of the patients with IE.
   B. Anaemia is seen in 70–90% of the cases.
   C. The sedimentation rate is elevated.
   D. Proteinuria occurs in 50–65% of cases.
3. Each of the following is true in relation to infective endocarditis, *except*:
   A. Transthoracic echocardiography (TTE) has a specificity of 98% and sensitivity of 65% for vegetations.
   B. Transesophageal echocardiography (TEE) is highly sensitive for detecting vegetations – sensitivity 75–100% and specificity of 94% for perivalvular extension.
   C. When both TEE and TTE studies are negative, there is a 95% negative predictive value.
   D. A repeat TTE study is not warranted even if there is a high clinical suspicion.
4. In the management and treatment of infective endocarditis, the following is true, *except*:
   A. Combination antibiotic therapy is almost always appropriate for IE.
   B. Antibiotic prophylaxis remains important for patients with high-risk cardiac condition.
   C. Heart failure during the early phase of the infection is not an indication for surgery.
   D. Rapid surgery should be performed if there has been an embolic episode.
5. The following require antibiotic prophylaxis before dental procedure, *except*:
   A. Mitral valve prolapse
   B. Prosthetic valve
   C. Past history of infective endocarditis
   D. Right ventricular hypertrophy

MCQ Answers

1 = C; 2 = A; 3 = D; 4 = C; 5 = D

Short Answer Questions

1. List four indications for surgery in the early phase of infective endocarditis.

SAQ Answers

1. (i) heart failure; (ii) perivalvular infection; (iii) large/mobile vegetations; (iv) prosthesis

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Coronary Artery Disease

4

Contents

Abstract

Coronary heart disease (CHD) is the largest cause of death and disability and the largest single cause of death in Australia and accounted for 21% of all deaths in 2000 and 19% of all deaths in 2004. A single aetiology is rarely found in the majority of old people with CHD. The risks for coronary artery disease increase with age. The damage to the endothelial lining is most often caused by a combination of the following: hypertension, high blood cholesterol, smoking and diabetes. This review discusses the risk factors followed by an update on the clinical management. A large proportion of elderly patients with myocardial ischaemia have atypical manifestations including dyspnoea and worsening heart failure in addition to an excess occurrence of unstable angina and non-Q wave myocardial infarction. Early diagnosis and prompt treatment are vital in patients with STEMI. Preventing heart disease is an important part of overall management.

Keywords

Coronary heart disease · Risk factors · Unstable angina · Acute coronary syndromes(ACS) · Unexpected sudden death · ST-elevation myocardial infarction (STEMI)

Introduction

In Australia, the incidence of coronary heart disease (CHD) in 2003 was an estimated 49,800 CAD events (non-fatal hospitalisations plus number of deaths in the population) among 40–90 year olds [1]. A 2004–2005 National Health Survey in Australia based on self-reporting revealed that 1.7% of those surveyed had manifestations of CHD, three-quarters of whom had angina and

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_3

one-third reported of having had a heart attack [1]. It is the largest cause of death and disability and the largest single cause of death in Australia and accounted for 21% of all deaths in 2000 [2, 3] and 19% of all deaths in 2004 [2]. CHD accounted for 51% of all cardiovascular deaths and half of them were from acute myocardial infarction [1].

In the United States, the incidence of CHD in 2004 was approximately 1 in 226 or 1.2 million people according to the American Heart Association [4]. Twenty percent of all hospitalisations for myocardial infarction (MI) and 30% of all MI-related hospital deaths occurred in patients above 80 years who constitute only 5% of the US population [5]. The prevalence of chronic ischaemic heart disease in men and women 65 years and over in the United States in 1995 was 83 per 1000 men and 90 per 1000 women. Among those 75 years of age and over, the prevalence was 217 per 1000 for men and 129 per 1000 for women [6].

The blood supply to the heart is from two main coronary arteries, the left and right. Both arise from the root of the aorta. The left coronary artery divides into circumflex and anterior descending branches that perfuse the greater part of the left ventricle and the left atrium. The right coronary artery supplies the inferior surface of the left ventricle, the right ventricle and the right atrium. Branches from both arteries penetrate the myocardium and form a dense capillary bed.

Risk Factors

A single aetiology is rarely found in the majority of old people with CHD. Risk factors for CHD can be categorised into non-modifiable and modifiable, and modification of some of these factors can reduce the risk of CHD (primary prevention) and will be just as helpful in secondary prevention. It is important to identify the non-modifiable risk factors (Box 1) for these may alert the clinician to potentially risk groups. Within this group, treatment of any modifiable factors may be of importance:

(i) Non-modifiable CAD risk factors

The risks for coronary artery disease increase with age. Men are at greater risk than women until women reach menopause when risks become equal for both. Family history is a well-known risk factor in the development of atherosclerosis, and a family history of familial hypercholesterolaemia carries a significant risk. Race may also be important.

(ii) Modifiable CAD risk factors (Box 1)

Among the modifiable CAD risk factors, particular attention is required to identify dyslipidaemia, hypertension and smoking. The Framingham study had shown that when these three risk factors are present, the heart attack rate was seven times greater than when none was present. The Framingham study demonstrated a near linear relationship between total cholesterol levels or LDL level and severity of the atherosclerosis as determined by the mortality rate from CHD and also association with other risk factors such as age, family history, gender and hypertension [7]. The development of CAD has also been shown to be linked with hypertension and smoking [3]. The damage to the endothelial lining is most often caused by a combination of the following: hypertension, high blood, cholesterol, smoking and diabetes [8].

Box 1 Modifiable Risk Factors and Non-modifiable Risk Factors

Dyslipidaemia
Hypertension
Smoking
Diabetes
Obesity
Physical inactivity
Stress
Alcohol consumption
Age
Gender
Family history
Ethnicity/race

The landmark INTERHEART study was a case-control study (15,152 incident cases of AMI and 14,829 controls matched by age and sex with no history of heart disease) that was undertaken in both developed and undeveloped countries (more than 50 countries). The study identified nine easily measured risk factors, namely, hypertension, diabetes, smoking, lipids, obesity, diet, physical activity, alcohol consumption and psychosocial factors that accounted for over 90% of the risk of acute myocardial infarction (AMI) [9, 10].

Dyslipidaemia. Abnormalities of serum lipids especially low-density lipoprotein (LDL) are regarded as atherosclerotic risk factors [11]. There is considerable evidence in support of lowering the lipids in primary and secondary prevention of CAD. Although there is limited data on such treatment strategies in the elderly, recent trials in the elderly have provided data to guide therapy in this population. In the INTERHEART study, the apoB/apoA1 ratio was the strongest factor predicting as opposed to any other cholesterol ratios for estimation of the risk of AMI in both sexes, at all ages and in all ethnic groups. Furthermore, it has the advantage that it can be measured in non-fasting blood samples. ApoA1 reflects the antiatherogenic properties of HDL cholesterol and ApoB the atherogenicity of triglycerides and small dense LDL particles.

Cigarette smoking has long been established as a risk factor for CHD. Smoking was the second strongest predictor, and the INTERHEART study showed that smoking one to five cigarettes daily increases the risk by 40% which increases further with the amount of tobacco smoked per day [9]. Moreover, it obviates the beneficial effects of aspirin and statin in secondary prevention.

Hypertension is present in more than two-thirds of patients older than 65 years, and elderly people are more likely to have poorly controlled blood pressure. It is a major risk factor at all ages for atherosclerosis and more important than hypercholesterolaemia after the age of 45 [12].

Diabetes potentiates the effects of hypercholesterolaemia and markedly increases predisposition to atherosclerosis. In the INTERHEART study, diabetes and hypertension may have been underestimated since these two factors were self-reported [9].

Obesity: The Framingham study revealed that being more than 30% overweight increased the mortality for ischaemic heart disease. The INTERHEART study revealed that abdominal obesity is a greater risk factor than BMI and indicated that the waist-to-hip ratio should replace BMI as an indicator of obesity [9].

Moderate consumption of alcohol raises the HDL level that has a protective effect.

Physical inactivity: Regular exercise reduces premature mortality from cardiovascular disease.

Diet: The INTERHEAT study found high intake of fruit and vegetables to be protective against myocardial infarction [9].

Psychosocial factors: There is a strong and consistent evidence of an independent causal association between depression, social isolation and lack of social support with CHD. The increased risk due to these psychosocial factors was found to be of similar order to the more accepted risk factors such as dyslipidaemia, hypertension and smoking [13]. A low socioeconomic status has been associated with increased CHD mortality [14]. The INTERHEART questionnaire included stress at work or home, financial stress, stressful events, depression and locus of control, and the results indicated that psychosocial factors may contribute a significant proportion of risk for AMI [9, 10].

Clinical Manifestations

Coronary heart disease embraces a wide spectrum of clinical manifestations from stable angina to acute coronary syndromes. Angina is a clinical syndrome with characteristic quality and duration of (i) discomfort in the chest, jaw, shoulder, back or arm, (ii) typically aggravated by exertion or emotional stress and (iii) relieved by nitroglycerin. The symptom complex has been grouped as typical angina, atypical angina or non-specific chest pain [15]. Definite angina satisfies all three

criteria stated above, atypical angina meets two of the characteristics and non-cardiac chest pain meets less than one of the characteristics [15]. The major adverse outcomes are unstable angina, myocardial infarction and sudden death due to arrhythmias.

The pain in unstable angina compared with stable angina is generally more severe and lasts longer, occurring spontaneously at rest, with less effort and is progressive. It is due to the rupture of the atheromatous plaque with platelet adhesion. The classic pathology of unstable angina is that of a non-occluding thrombus. The pain at rest is due to a number of mechanisms. The episodes of pain from myocardial ischaemia are caused by bursts of platelet emboli, spasm at the site of injury or intermittent growth of thrombus to occlude, followed by recanalisation by natural lysis [16]. NSTEMI has been considered as a more severe state of the same clinical syndrome [17].

The term acute coronary syndromes (ACS) encompasses the clinical manifestations for unexpected sudden death to unstable angina to ST-elevation myocardial infarction (STEMI) also referred to as major Q-wave myocardial infarction or non-ST-elevation acute coronary syndromes (NSTEACS) on the basis of ECG findings. NSTEACS is subdivided into non-STEMI and referred to as non-Q myocardial infarction and unstable angina according to the cardiac enzyme results. In three-quarters of the patients with ACS, there is plaque disruption of a minor stenotic lesion and in the remainder plaque erosion in a more severe stenotic lesion [18, 19]. Sudden death without previous symptoms occurs in about 10% of patients with CHD. If the patient presents within 3 h of evolving acute myocardial infarction and electrocardiogram shows unequivocal ST-segment elevation, the patient is subjected to thrombolysis or coronary angioplasty.

Atypical presentations are more common in the elderly with MI and symptoms may be more subtle [20]. Dyspnoea, fatigue and heart failure symptoms were more frequently the first symptoms than typical chest pain unlike that in younger patients [21]. In the elderly, STEMI was more common, and non-STEMI was diagnosed and more common in women and in patients previously diagnosed with ischaemic heart disease, diabetes and hypertension [21] so were the presence of cerebral and peripheral vascular diseases and renal failure [22].

Primary diagnostic precondition is differentiating ACS from non-cardiac chest pain. Patients with all three characteristics of typical angina have a possibility of having ACS. The initial assessment of a patient presenting with chest pain is a history that focuses on the anginal symptoms and risk factor evaluation, physical examination, electrocardiogram and biomarkers of cardiac injury with early risk stratification. Risk stratification is of vital importance in patients presenting with UA/NSTEMI [17]. The primary aim is in evaluating patients with non-STEMI. The aim is to exclude or confirm acute myocardial infarction and risk stratification for further investigations and treatment. The AHCPR categorised UA for death or MI into low, medium and high largely based on the history, physical and ECG findings [23].

The likelihood of ACS (low, intermediate, high) should be determined in all patients presenting with chest pain. TIMI (Thrombolysis in Myocardial Infarction) score and GRACE (Global Registry of Acute Cardiac Events) score are the best systems for risk stratification for unstable and non-STEMI. The seven TIMI score predictors are age 65 years or older, at least three CAD risk factors (family history of CAD, hypertension, hypercholesterolaemia, diabetes and current smoking), known coronary stenosis of 50% or more, use of acetylsalicylic acid in the past 7 days, at least two severe angina episodes in the previous 24 h, ST changes on ECG at presentation and elevated serum cardiac markers [24]. The variables of the GRACE risk score are age, heart rate, systolic blood pressure, cardiac arrest, Killip class, serum creatinine, ST-segment changes and cardiac biomarkers [25].

A large proportion of elderly patients with myocardial ischaemia have atypical manifestations including dyspnoea and worsening heart failure in addition to an excess occurrence of unstable angina and non-Q wave myocardial infarction [26, 27]. In the elderly with MI, there is a frequent substitution of dyspnoea for chest

discomfort, and this atypical presentation especially in women may partly explain the high rate of unrecognised MI in this age group [28]. Patients presenting with acute pulmonary oedema are generally older than those manifesting typical anginal symptoms [29, 30].

Patients who have acute myocardial infarction often delay hospital admission. Early treatment in acute myocardial infarction is crucial. There have been several studies on delayed arrival in the hospital with suspected myocardial infarction. The reasons for delay have been attributed not only to clinical and logistics factors but also to race, female sex, older age, diabetes and socioeconomic characteristics [31, 32]. There have been several suggestions to address this such as educational interventions; targeting specific populations, namely, the elderly, female and patients with cardiac risk factors; and the prompt use of emergency medical transport services [26].

Management

Early diagnosis and prompt treatment is vital in patients with STEMI. Several randomised trials have validated primary angioplasty and stents as the optimal therapy for these patients as primary percutaneous coronary intervention (PCI) yields >90% TIMI 3 flow in the infarct-related vessel compared to about 50% after thrombolytic therapy [33]. If STEMI patients cannot be treated with PCI, thrombolytic therapy is the preferred initial therapy [33]. After thrombolysis, it is expedient for patients to be referred for coronary angiogram and revascularisation between 2 and 24 h [34]. Glycoprotein IIb/IIIa inhibitors (tirofiban, eptifibatide or abciximab) are beneficial in STEMI patients, and intracoronary bolus administration is usually reserved for high-risk patients [33] especially patients with diabetes undergoing PCI. Antiplatelet drugs improve the survival of patients with acute coronary syndrome. Aspirin (300 mg) should be administered immediately and is usually continued indefinitely. Clopidogrel can be used if there is aspirin allergy. A loading dose of 300–600 mg clopidogrel as early as possible is given prior to primary PCI thereafter a maintenance dose of 75 mg/d and continued for this regimen long term, for example, a year [35]. Granules containing adenosine diphosphate (ADP) bind to the P2Y12 receptor on the surface of the platelets initiating platelet aggregation. Two newer ADP-receptor inhibitors including prasugrel and ticagrelor have been studied in STEMI patients compared to clopidogrel [33]. Clopidogrel and prasugrel are thienopyridines and they bind to the P2Y12 receptor irreversibly. Whereas ticagrelor is a non-thienopyridine, it is a reversible P2Y12 receptor antagonist [33]. Randomised trials have shown the newer antiplatelet agents compared to clopidogrel to be superior in patients with STEMI and would benefit more from them following primary PCI [33]. A loading dose of 150 mg of ticagrelor is administered followed by 90 mg twice daily. Maximal platelet inhibition is achieved in approximately 30 min with prasugrel [36], whereas ticagrelor takes 2 h and clopidogrel takes 2–8 h depending on the dose [37]. The risk of haemorrhage is higher with the newer antiplatelet agents compared to clopidogrel. Bivalirudin, a transient and reversible thrombin inhibitor, should be considered as the preferred anticoagulant for patients undergoing primary PCI [33].

In patients with NSTEMI or unstable angina in addition to aspirin in combination with clopidogrel and anticoagulant therapy, a platelet glycoprotein (GP) IIb/IIIa receptor antagonist is administered if PCI is to be performed [35]. Anticoagulant drugs reduce the risk of thromboembolic complications and are done with the use of low molecular weight, unfractionated heparin (dalteparin, enoxaparin or fondaparinux) for a period of usually 8 days. Medium- to high-risk patients should be considered for early coronary angiography and revascularisation. For low-risk patients' medical treatment and for those who do not respond to medical treatment, coronary angiography and revascularisation should be considered.

There are significant differences in coronary artery lesions between younger and older persons with the latter more likely to have calcified, ostial, tortuous, multi-vessel and left main

lesions [38]. Older persons are also more likely to have co-morbid conditions such as renal impairment, cognitive impairment and frailty, and as a result, they are under-represented in clinical revascularisation trials. They also have higher risk of complications during and after coronary revascularisation. Evidence however suggests older persons derive significant benefits, both in terms of mortality and quality of life, from revascularisation as do the younger cohort.

The Trial of Invasive versus Medical Therapy in Elderly Patients with chronic symptomatic CAD (TIME) showed that among 305 patients 75 years or over with symptomatic CAD, investigation and treatment group had better symptom relief and quality of life in addition to fewer major events (49% vs. 19%) [39]. Evidence from the GRACE registry which included over 15,000 patients over the age of 70 with non-ST-elevation MI showed significant differences in in-hospital mortality, combined end point of death, myocardial infarction and stroke at 6 months between groups treated with PCI versus medical therapy [40]. In a meta-analysis which included 410 octogenarians with STEMI, PCI was also shown to be superior to thrombolysis in having a lower incidence of all-cause mortality (18.3% vs. 26.4%) at 30-day follow-up [41]. It must be noted however that subjects included in these studies are highly selected.

There is some evidence to suggest that drug-eluting stents reduce MI and target lesion revascularisation but not all-cause mortality, stroke or major haemorrhages [42]. The choice of device should consider the nature of the lesion, the underlying co-morbidities and whether there are relative or absolute contraindications for dual antiplatelet therapy. The use of a radial versus femoral access has been shown to reduce the rate of local vascular complications [43].

With the ageing of population, almost 25% of all patients undergoing CABG are >70 years of age. In spite of the widespread reluctance of subjecting an older person to cardiac bypass surgery due to the increased risk and slower post-operative recovery period, appropriately selected older subjects can derive similar benefit, in terms of mortality and health-related quality of life from cardiac surgery. In a review of 18 studies performed in a number of countries, elderly patients have improved early and late HRQOL following CABG, better post-operative in comparison to pre-operative HRQOL scores and attain similar HRQOL in aged-matched general population [44]. Potential patients for CABG should be evaluated on the basis of the cognitive, functional state as rather than purely on their chronological age.

Prevention

Preventing heart disease is an important part of overall management. One concept that has been advanced in Europe and particularly in the UK is total risk management. The concept is a multifactorial assessment and intervention on the basis of absolute risk. The European Society of Cardiology task force report had defined priorities for coronary prevention [45]. In one category of patients with established coronary disease or any other symptomatic manifestation of atherosclerosis and a second category comprising healthy individuals who are at high risk of developing coronary disease, intervention in both groups should take account of all risk factors and not a single one in isolation. There is no distinction between the groups which should be managed equally. The claim is that the distinction between primary and secondary prevention is artificial in biological terms and that common goals should be set [45]. Total risk management directs that individuals with symptomatic atherosclerotic disease or who are asymptomatic or those at high absolute risk should all receive similar lifestyle guidance, have their risk factors reduced to the same targets and, where appropriate, be offered proven drug therapies [46]. It tends to avoid treatment of single risk factors in people at low multifactorial risk (Box 2).

Box 2 Primary Prevention of CAD
Cessation of smoking
Avoidance of excessive drinking
Regular exercise
Eat balanced diet, low-fat diet
Avoid overweight and obesity

(*continued*)

Box 2 Primary Prevention of CAD (continued)
Have a regular life and manage stress
Regular follow-up for regular illnesses, e.g. hypertension, diabetes, dyslipidaemia

Smoking: Adaptation of measures to quit smoking which are effective in younger individuals has also been proved to be equally effective in the elderly cardiovascular patient. These include physician's advice, behavioural counselling, self-help materials, telephone counselling and the use of pharmacological therapies [47, 48].

Hypertension: Hypertension is a major risk factor in coronary heart disease and is common among the elderly of both sexes. Systolic blood pressure is more predictive of risk than diastolic blood pressure; in the elderly, elevated systolic blood pressure has more significance than diastolic blood pressure. The Systolic Hypertension in the Elderly Program (SHEP) [49] and the European Trial on Hypertension in the Elderly [50] trials were conducted in elderly patients with isolated hypertension. The SHEP trial at the end of 5 years revealed a statistically significant reduction in adverse events related to coronary heart disease, congestive heart failure and overall cardiovascular disease following treatment of the hypertension in the elderly with isolated hypertension. The European trial stopped after 2 years because of a marked decrease in non-fatal and total strokes and a trend towards reduction of coronary artery disease and heart failure although no statistical significance was achieved. The SHEP trial also demonstrated that antihypertensive therapy reduced coronary artery disease in elderly patients with normal or high cholesterol.

Dyslipidaemia: There is strong evidence supporting lipid lowering in the primary and secondary prevention of CHD. Because these studies have not been specifically oriented towards the elderly, the value of such therapy in older individuals has been questioned. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) [51] revealed a significant reduction in rates of CHD-related mortality and non-fatal MI in high-risk patients 70 years and older with pravastatin. A subgroup analysis of the Heart Protection Study [52] supported the use of statins in elderly patients with CHD. Simvastatin significantly reduced rates of all-cause mortality, coronary death and non-fatal MI in patients older than 70 years including patients with LDL cholesterol levels less than 3.00 mmol/L.

Diabetes: The prevalence of diabetes is increasing, and diabetes is a strong predictor of recurrent ischaemic events in patients with CHD. The recommended interventions are similar to all age groups and include good glycaemic control, use of pharmacological therapies aimed at reducing the HbA1c level to less than 7% and achieving a near-normal fasting blood sugar level, dietary counselling, weight control and exercise.

Physical Activity: Reduces the chance of being overweight, decreased blood pressure and a more favourable lipid profile. Brisk walking for about 30 min on most days is recommended.

Impact

In the UK, according to the British Heart Foundation [53], 180,000 people died of cardiovascular disease and around 80,000 of them are from coronary heart disease. Likewise in the European Union, CHD is the most common cause of death [4]. The cost remains an enormous problem in almost every nation. It is the cause of premature death and disability amounting to 36% of all hospitalisation for cardiovascular disease in Australia [1]. The annual cost equates to 2.8% of the total recurrent health expenditure which includes the cost of specialist medical services, hospital stays and medications [3], and the direct health system costs in Australia was $630 million in 1993–1994 [2]. This is considered to be the average indication of the average cost, even today [2]. In the UK, CHD costs over 1.7 billion pounds per year [53] (Box 3).

Box 3 Key Points: Coronary Artery Disease
A large proportion of elderly patients with myocardial ischaemia have atypical

(*continued*)

Box 3 Key Points: Coronary Artery Disease (continued)

manifestations including dyspnoea and worsening heart failure in addition to an excess occurrence of unstable angina and non-Q wave myocardial infarction [27, 28].

Risk stratification is of vital importance in patients presenting with UA/NSTEMI [17].

Early treatment in acute myocardial infarction is crucial.

Total risk management directs that individuals who are asymptomatic or those at high absolute risk should all receive similar lifestyle guidance, have their risk factors reduced and where appropriate be offered proven drug therapies [47].

Multiple Choice Questions

1. The following complications of acute myocardial infarction are true, except:
   A. Mitral regurgitation
   B. Rupture of the papillary muscle
   C. Cardiac failure
   D. Pneumonia
2. A large proportion of elderly with myocardial ischaemia have atypical manifestations. The following are true, except:
   A. In the elderly with myocardial ischaemia, there is a frequent substitution of dyspnoea for chest discomfort.
   B. The elderly with myocardial ischaemia arrive early in the hospital.
   C. Patients presenting with acute pulmonary oedema are generally older.
   D. Elderly patients with myocardial ischaemia have an excess occurrence of unstable angina.
3. The following with regard to risk factors for coronary artery disease (CAD) are true, except:
   A. Among the modifiable risk factors, particular attention is required to identify dyslipidaemia, smoking and hypertension.
   B. In the Framingham study when the above-mentioned risk factors are present, the heart attack rate is seven times greater than when none are present.
   C. Diabetes is a strong predictor of recurrent cardiovascular events in patients with CAD.
   D. Quitting smoking by elderly cardiovascular patient is not as effective as in younger individuals.

MCQ Answers

1 = D; 2 = B; 3 = D

Short Answer Questions

1. List four complications of the atheromatous plaque.
2. List four functions of the vascular endothelium.

SAQ Answers

1. (i) Calcification of the plaque; (ii) Ulceration or rupture; (iii) Thrombosis; (iv) Haemorrhage into the plaque
2. (i) Prevents intravascular clotting; provide a permeability barrier; regulate vascular tone; produce NO

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Valvular Heart Disease in the Elderly

5

Contents

Abstract

Degenerative aetiology predominates in valvular heart disease. This review summarises the main group of valvular diseases with the main focus on their management. Aortic stenosis increases in frequency with age, and the important causes are the degenerative calcifying valves, congenital abnormalities and rheumatic in origin. About half the patients with AS die suddenly. The key symptoms indicating intervention are angina, exertional syncope and heart failure, but the ideal management of severe aortic stenosis with left ventricular dysfunction is controversial. Transcatheter aortic valve replacement (TAVR) is an option for patients with high or very high risk for surgical aortic valve replacement. Aortic valve replacement is indicated in severe AR who are symptomatic and in patients with severe AR who are asymptomatic but with left ventricular systolic dysfunction. Surgery is indicated in patients with severe MR with symptoms, and the factors influencing the timing of intervention are the symptoms, left ventricular ejection fraction, atrial fibrillation and pulmonary hypertension. Surgery in mitral stenosis depends on the symptoms right ventricular function, and pulmonary artery pressure.

Keywords

Aortic stenosis · Aortic regurgitation · Mitral regurgitation · Mitral stenosis · Transcatheter aortic valve replacement · Percutaneous mitral balloon valvuloplasty

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_5

Introduction

According to the European Heart Society on valvular heart disease (VHD), degenerative aetiology predominates [1]. The prevalence of VHD increases with age, increasing from 0.7% in the 8–44 group to 13% in the over 75 years of age [2]. Many elderly have either mitral or aortic valvular disease due to degenerative valvular disease. Two to 3% of the 75 years and older are affected with calcific aortic stenosis, and of the 1–2% of the population with bicuspid aortic valves, about half develop aortic stenosis and one-third develop aortic regurgitation [3]. In the elderly, calcific aortic stenosis and mitral regurgitation due to mitral valve prolapse are the most frequently occurring lesions although rheumatic mitral stenosis and aortic incompetence are not uncommon [4, 5]. Aortic stenosis occurs in 2%, and in subjects above 75 years, sclerosis was present in 37% and stenosis in 2.6% [6]. In the elderly, aortic stenosis and ischaemic mitral regurgitation are the most common valvular diseases, and the overall prevalence in the over 70 years with clinically significant aortic stenosis is approximately 1–3% [2]. (Table 1).

Aortic Stenosis

Aortic stenosis increases in frequency with age, and the important causes are the degenerative calcifying valves, congenital abnormalities and rheumatic in origin. Although calcific aortic valve disease is common in older age group, it is not a consequence of ageing [6, 8, 9]. Aortic valve sclerosis (AVS) in the absence of flow obstruction is common in the elderly. Congenital bicuspid aortic valves are the commonest cause of AS and

Table 1 Causes of valvular heart disease in the elderly

Cause	Lesions	Pathology
Primary		
Congenital valve abnormalities (bicuspid and tricuspid aortic valves)	AR, AS	Fibrosis, rigidity and calcification of deformed valves
Degenerative heart disease	AS, MR occ. MS	Calcification of the valve leaflets in AS
		Calcification of mitral annulus in MI rarely extend onto the leaflets,causing MS
Myxomatous degenerative	MR, AR, TR	Mucoid degeration of the valve cusps eventually to prolapse, chordal rupture and dilatation of aortic root may occur
Infective endocarditis	MR, AR	Leaflet perforation, prolapse, chronic scarring
Rheumatic heart disease	MR, AR, AS	Commissural fusion, fibrosis, calcification of leaflets and chordae
Ischaemic heart disease	MR	Papillary muscle dysfunction (fibrosis), rupture
Connective tissue disorders	AR	Medial disease, aortic root dilatation, aortic dissection
Other		
Amyloid rarely	MS	Valvular thickening
Carcinoid	TS,TR	Stenosis of valve or incompetence
Secondary		
LV dilatation of mitral annulus secondary to CAD, aortic valve disease, dilated cardiomypopathy	MR	Pathology as varied as the cause
Dilatation of the aorta		
Hypertension, aneurysm of aorta	AR	
RV enlargement		
Pulmonary hypertension	TR	

Information source: Curtin and Griffin [7]
AR aortic regurgitation, *AS* aortic stenosis, *MR* mitral regurgitation, *MS* mitral stenosis, *TR* tricuspid regurgitation, *TS* tricuspid stenosis

accounts for 40% in the United Kingdom [2]. In aortic stenosis of rheumatic origin, there are adhesions with fusion of the commissures and cusps, calcification, scarring and retraction of the leaflet resulting in reduction in the valve orifice.

Symptoms and Signs

The majority of patients with AS are asymptomatic. The onset of syncope, angina and symptoms of heart failure points to advanced disease, and the prognosis is poor. About one-third of the patients with symptomatic AS experience syncope on exertion. Syncope with AS may also be due to ventricular fibrillation. Angina is an early symptom, and sometimes it may be difficult to decide whether it is due to critical AS or to coexisting coronary artery disease. Heart failure is precipitated by the poor diastolic filling of the poorly compliant ventricle. The patient may remain asymptomatic for years for the compensatory concentric left ventricular hypertrophy allows the pressure overloaded ventricle to maintain a stroke volume with moderate increases in diastolic pressure [3].

In the elderly, the upstroke may be normal because of the poorly compliant carotid artery or if there is accompanying aortic regurgitation. In severe cases the blood pressure is low, the pulse pressure small, a slow rising small volume carotid pulse and a systolic thrill. The stiff non-compliant carotid arterial wall may mask these findings. A harsh loud ejection systolic murmur maximally heard in the right sternal edge radiates to the neck and often transmitted to the lower left sternal border and to the cardiac apex [3] simulating the murmur of mitral regurgitation. In the elderly, the murmur of calcific AS is heard predominantly at the apex, and the degree of valvular calcification correlates with the severity of the stenosis. The longer the murmur, the longer it takes to peak more the stenosis. The basal murmur can soften or be absent in critical stenosis due to decreased cardiac output. The aortic second sound is soft and may be inaudible when the stenosis is severe because of the increased rigidity and calcification of the valves. In the elderly, the murmur of AS may lose its qualities, and the severity of AS is best judged on other grounds.

X-rays may show calcification of the aortic cusps. The electrocardiogram shows various degrees of left ventricular hypertrophy and the finding of a 'strain pattern' (ST depression with inverted T waves) signifying severe stenosis and endocardial ischaemia and fibrosis. Doppler echocardiography is used to diagnose and determine severity [10] by determining outflow tract pressure gradients and also used to detect coexisting AR. Cardiac catherisation is required in patients with severe AS to identify coexisting coronary artery disease which may require coronary artery bypass surgery simultaneously.

About half of the patients with AS die suddenly. Patients with severe stenosis should refrain from strenuous activity to avoid sudden death. Symptomatic patients have a mortality of 50% at 1 year. Symptomatic severe AS and patients with severe AS and left ventricular systolic dysfunction [11] are treated with surgery even in the elderly [10, 12] as average survival falls rapidly [12]. The key symptoms indicating intervention are angina, exertional syncope and heart failure [13], but the ideal management of severe aortic stenosis with left ventricular dysfunction is controversial [12]. High mortality is associated with development of heart failure in patients with aortic stenosis [12]. In one study, 33% of patients with severe aortic stenosis were denied surgery due to older age, and left ventricular dysfunction and comorbidity did not play a substantial part [14].

Open aortic valve replacement remains the gold standard for end-stage aortic stenosis and improves survival and quality of life in elderly patients. There is no age limit for aortic valve surgery in patients with aortic stenosis in the absence of comorbidities [15]. For the elderly with severe aortic stenosis and comorbidities, open cardiac surgery carries a high operative risk and is contraindicated. Concurrent coronary bypass surgery may increase the risk of postoperative complications and death. Balloon aortic valvuloplasty has a high rate of restenosis in more than two-thirds of patients [16] within 6 months [17] and a high post-hospital complications and mortality of 10–25% [17]. In a study of 92 patients 80 years and older with severe AS who had percutaneous balloon valvuloplasty, the majority of the surviving 44 patients experienced marked

symptomatic improvement [18]. It is used in high-risk elderly patients who are not considered for surgery or an emergency measure pending valve replacement. For older patients, replacement with bioprosthetic valves for good surgical candidates is an alternative for there would be no need for warfarin therapy [13]. Transcatheter aortic valve replacement (TAVR) is an option for patients with high or very high risk for surgical aortic valve replacement [19]. According to ACC/AIHA guidelines, prophylactic treatment for infective endocarditis (IE) is no longer required; however, IE prophylaxis is mandatory for patients with prosthetic valves including anticoagulation with warfarin for those with mechanical valves [3, 20]. It is noteworthy that statins may retard the progression of aortic stenosis [3].

Aortic Regurgitation

Aortic regurgitation (AR) could present in an acute or chronic form and due to aortic root disease or leaflet pathology [21, 22]. The causes are shown in Box 1.

Box 1 Causes of Aortic Regurgitation

Acute
- Infective endocarditis
- Trauma
- Aortic dissection

Chronic
- Isolated severe AR (aortic root annular dilatation? – medial disease)
- Rheumatic heart disease
- Congenital bicuspid valve
- Myxomatous degeneration
- Previous infective endocarditis
- Severe systemic hypertension

Symptoms and Signs

AR affects men more than women. Patients with mild to moderate AR are often asymptomatic for many years and may remain so even in old age. Palpitations may occur due to the forceful contraction of the ventricle, and in a small number, angina may occur in the absence of coronary artery disease. In the symptomatic patients, dyspnoea, orthopnoea and paroxysmal nocturnal dyspnoea may herald heart failure.

The pulse has a quick rise with a rapid fall away with a large volume (water hammer pulse, collapsing pulse). The diastolic blood pressure is low and the systolic pressure higher than normal with a large pulse pressure. The large carotid pulsations in the neck are called Corrigan's sign. The sharp sound heard over the femoral pulse is called pistol-shot sound, and the systolic murmur heard over the femoral artery distal to the finger pressure is called Duroziez's murmur.

On auscultation, there is a high-pitched diastolic murmur best heard over the left sternal border in aortic leaflet disease and loudest in the right sternal border in aortic root disease. The murmur may be accompanied by a diastolic thrill and a systolic murmur of increased aortic outflow. The forward ejection murmur and the backward regurgitant murmur are called a to and fro murmur. The diastolic murmur may be inaudible or missed, and the systolic murmur may be the pointer to aortic regurgitation and indicates further investigations [23]. Sometimes a mid-diastolic rumble like in mitral stenosis is heard at the apex [3] because the aortic regurgitant stream prevents the opening of the anterior mitral leaflet (Austin Flint murmur).

X-ray shows cardiac enlargement with dilated aorta. Linear calcification in the ascending aorta is seen in syphilitic AR. The electrocardiogram shows left ventricular hypertrophy. The underlying causes should be treated, for example, AR following dissection requires surgery. The severity of the leak can be determined by Doppler imaging and functional anatomy of the valve and aortic root by ECHO [3].

In patients with moderate to severe heart failure, aortic valve replacement is indicated after appropriate medical therapy for heart failure. Aortic valve replacement is indicated in patients with severe AR who are symptomatic and in patients with severe AR who are asymptomatic but with left ventricular systolic dysfunction. Bioprosthetic valves are favoured in the elderly because they do not require anticoagulant therapy. According to

the new ACC/AHC guidelines, IE prophylaxis is no longer required [20].

Mitral Regurgitation

Moderate to severe MR is present in approximately 10% of the general population over the age of 75 years [24]. The causes are shown in Box 2.

Box 2 Causes of Mitral Regurgitation

Acute
- Trauma
- Infective endocarditis
- Myocardial infarction
- Systemic hypertension

Chronic
- Degenerative mitral annular calcification
- Coronary artery disease (papillary muscle dysfunction, rupture, rupture of chordae, ischaemia and necrosis)
- Myxomatous valvular degeneration – mitral valve prolapse
- Rheumatic heart disease (post-inflammatory scaring)
- Mitral valve annular dilatation secondary to left ventricular and left auricular enlargement (aortic valve disease, coronary artery disease), dilated cardiomyopathy
- Previous infective endocarditis
- Hypertrophic obstructive cardiomyopathy (due to systolic anterior movement of the mitral valve).

Symptoms and Signs and Management

In acute MR, there will be a new apical systolic murmur often with a thrill and sinus tachycardia. In chronic MR, there is an apical pansystolic murmur and often with a soft first heart sound.

Surgery is indicated in patients with severe MR with symptoms and the factors influencing the timing of intervention are the symptoms, left ventricular ejection fraction, atrial fibrillation and pulmonary hypertension. In the elderly, mortality is increased by comorbidities such as coronary artery disease, cerebrovascular disease, heart failure, atrial fibrillation and renal insufficiency [25]. Mitral valve repair is the operation of choice in patients with suitable mitral valve anatomy [26]. For suitable mitral regurgitation patients, there are two main approaches, mitral valve remodelling and edge to edge repair and mainly used in degenerative mitral valve disease, mitral valve prolapse [15]. Chikwe et al. [27] studied the results of 322 octogenarians; the larger group were those with degenerative and those with functional MR. About half of the combined series had coronary artery bypass grafting as well; a third had concomitant tricuspid valve repair. The study confirmed that the overall mortality was high in octogenarians with mitral valve surgery. Patients with MR repair compared to valve replacement were associated with higher survival both early and late postoperatively. However the durability of valve repair remains unclear [28]. There are reports that transcatheter techniques associated with low procedural risks can be beneficial in the very old population [29, 30].

Mitral Stenosis

Mitral stenosis is predominantly due to rheumatic heart disease and is usually identified before old age. A rare cause is mitral annular calcification and is more common in elderly women than men.

Symptoms and Signs

Significant mitral stenosis (MS) may be found in patients with little or no symptoms. A loud first heart sound with an opening snap is heard in the apex. In the left lateral position, an apical rumbling diastolic murmur with a presystolic accentuation could be heard at the apex if the patient is in the sinus rhythm. Atrial fibrillation is commonly encountered in the elderly patient. With valve calcification, the diastolic murmur and the opening snap becomes softer and may disappear.

X-ray shows a straight left cardiac border due to the dilatation of the left auricular appendage. A double shadow of enlarged left auricle is characteristic along the right cardiac border. Electrocardiogram may show widely notched P waves, right ventricular hypertrophy and atrial fibrillation if present.

Surgery in mitral stenosis depends on the symptoms, right ventricular function and pulmonary artery pressure. Three potential interventions are available: percutaneous mitral balloon valvuloplasty (PMBV), surgical mitral commissurotomy and mitral valve replacement (MVR) [7]. Percutaneous mitral balloon valvuloplasty (PMBV) is indicated for moderate to severe MS where valve morphology is favourable and in the absence of left atrial thrombus or moderate to severe MR. Mitral valve repair or replacement is indicated when PMBV is not available or valve morphology is not suitable or is contraindicated because of left atrial thrombus. There is a high risk of thrombosis with prosthetic valves which makes anticoagulation mandatory [26].

Impact

There is an increase in the number of elderly patients affected by valvular heart diseases and is a significant cause of morbidity and mortality [31]. Advanced age is one of the more important risk factors of mortality and a leading cause of morbidity after cardiac surgery [32]. Transcatheter aortic valve replacement is a therapeutic option for selected patient who is at high risk for surgery. The burden of disease among the elderly with aortic stenosis is significant with a pooled prevalence of 3.4%, and nearly 27,000 patients become eligible annually [19] (Box 3).

Box 3 Key Points: Valvular Diseases in the Elderly

With the increase in the number of elderly population, valvular heart disease due to degenerative calcification, myxomatous degeneration, papillary muscle dysfunction and infective endocarditis among others is increasing.

Box 3 Key Points: Valvular Diseases in the Elderly (continued)

Aortic stenosis increases in frequency with age, and the important causes are the degenerative calcifying valves, congenital abnormalities and rheumatic in origin. The onset of syncope, angina and symptoms of heart failure points to advanced disease and the prognosis is poor.

Open aortic valve replacement remains the gold standard for end-stage aortic stenosis and improves survival and quality of life, and the perioperative mortality is 4–5% in elderly patients.

There is no age limit for aortic valve surgery in patients with aortic stenosis in the absence comorbidities.

Aortic valve replacement is indicated in severe AR who are symptomatic and in patients with severe AR who are asymptomatic but with left ventricular systolic dysfunction.

Chronic MR may result from disruption or injury of these elements, namely, the annulus, valve leaflets, chordae, papillary muscles and left ventricle.

One study confirmed that the overall mortality was high in octogenarians with mitral valve surgery.

Mitral valve replacement is indicated for mitral stenosis when percutaneous mitral balloon valvuloplasty is not available or valve morphology is not suitable.

Multiple Choice Questions

1. The following with regard to aortic stenosis are true, *except*:
   A. The bicuspid valve comes to attention in the younger elderly in the fifth and sixth decade and the tricuspid in the seventh decade or later.
   B. Although often considered ‘degenerative’, recent evidence suggest that aortic valve stenosis may denote an auto-immune reaction to antigen on the valve.
   C. The basal murmur can increase in critical stenosis.

D. Doppler echocardiography is used to determine outflow pressure gradients and also coexisting aortic incompetence.

2. The following signs and symptoms of aortic stenosis (AS) are true, *except*:
   A. The onset of syncope, angina and symptoms of heart failure points to advanced disease, and the prognosis is poor.
   B. Syncope in AS may also be due to ventricular fibrillation.
   C. In the elderly, the murmur of AS may lose its qualities, and the severity of AS is best judged on other grounds.
   D. The aortic second sound is loud and audible when the stenosis is severe.
3. The following with regard to diagnosis and management of aortic stenosis are true, *except*:
   A. Cardiac catheterisation is required in patients with severe AS to identify coexisting coronary artery disease.
   B. Balloon valvuloplasty has a low rate of restenosis and low post-hospital mortality.
   C. Aortic valve replacement improves survival and quality of life, and the perioperative mortality is 4–5% in elderly patients.
   D. Doppler echocardiography is used to determine outflow tract gradients and coexisting aortic regurgitation.
4. The following statements are true regarding aortic regurgitation(AR), *except*:
   A. Isolated severe aortic regurgitation is from aortic root/annular dilatation.
   B. Patients with mild to moderate AR are often asymptomatic for many years and may remain so even in old age.
   C. Sometimes a diastolic rumble like in mitral stenosis is heard at the apex.
   D. Bioprosthetic valves are not favoured in the elderly because they require anticoagulant therapy.
5. The following in mitral incompetence are true, *except*:
   A. In the elderly, myxomatous degeneration of the valves is an important cause of mitral valve prolapse.
   B. In acute mitral regurgitation, there will be a new apical systolic murmur often with a thrill.
   C. In chronic mitral incompetence, there is an ejection systolic murmur and often with a loud first sound.
   D. Mitral valve repair is the operation of choice in patients with suitable mitral valve anatomy.
6. The following in relation to mitral stenosis are true, *except*:
   A. Little more than half the patients with rheumatic heart disease do not give a history of rheumatic fever or chorea.
   B. With valve calcification, the diastolic murmur and opening snap become louder.
   C. There is a high risk of thrombosis with prosthetic valves and anticoagulation is mandatory.
   D. Significant mitral stenosis may be found in patients with little or no symptoms.

MCQ Answers

1 = C; 2 = D; 3 = B; 4 = D; 5 = C; 6 = B

Extending Matching Questions

A. Tricuspid incompetence
B. Aortic regurgitation
C. Mitral regurgitation
D. Ventricular septal defect
E. Mitral stenosis
F. Syphilitic aortitis
G. Hypertension
H. Aortic stenosis
I. Tricuspid stenosis

Match the murmurs with the most characteristic cardiac disorder. Use each answer only once:

1. In the lateral position, an apical rumbling murmur with a presystolic accentuation at the apex
2. An apical pansystolic murmur and often with a soft first heart sound
3. A high-pitched diastolic murmur best heard over the left sternal border
4. A high-pitched diastolic murmur loudest in the right sternal border
5. A harsh ejection systolic murmur heard in the right sternal edge radiating to the neck and to the cardiac apex

6. A systolic murmur with a ringing second sound in the aortic area

EMQ Answers

1 = E; 2 = C; 3 = B; 4 = F; 5 = H; 6 = G

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Hypertension in the Elderly

6

Contents

Abstract

In patients with sporadically elevated blood pressure or white coat hypertension, a 24-h ambulatory BP monitoring is useful. This chapter will provide an update in the clinical management of hypertension in the elderly. Most of the causes of secondary hypertension in the younger adult are relatively uncommon in the elderly with the exception of renal artery stenosis. Evaluation of target organ damage begins with a physical examination. Hypertensive retinopathy together with left ventricular hypertrophy and renal impairment are considered as an indicator of target organ damage There is positive evidence that treating hypertension in the elderly and very elderly provides clinical benefits. Several trials have indicated that lowering the systolic blood pressure (SBP) to less than 140 mmHg as recommended by the prevailing guidelines is not upheld by evidence in the elderly and does not benefit the elderly and the very elderly.

Keywords

White coat hypertension · Isolated systolic hypertension · Sodium sensitivity · Hypertensive retinopathy · Renal artery stenosis

Introduction

In the elderly, hypertension is associated with isolated systolic hypertension, "white coat effect" and sodium sensitivity [1]. An intrinsic part of management is to confirm elevated blood pressure by multiple determinations. Hypertension is diagnosed when systolic pressure is >140 mmHg or diastolic 90 mmHg or both. In the elderly, at least two seated measurements of the blood pressure must be made, remeasured 1 and 3 min after standing, measured in both arms [2]. In patients with sporadically elevated blood pressure or white coat hypertension, a 24-h ambulatory BP monitoring is useful (normal ambulatory blood

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_4

pressure but with elevated reading in the clinic) [2].

Clinical Evaluation

A focussed history, physical examination and basic laboratory investigations should be done in all patients with a blood pressure of 140/90 mmHg. Due consideration should be given to identify any additional cardiovascular risk factors [3] and overall estimate of cardiovascular risk and furthermore to ascertain target organ damage [3]. Careful history, a physical examination and a few simple laboratory tests will help in the diagnosis of secondary hypertension. The history should include past history and current symptoms of cardiovascular disease or renal disease and other significant illnesses. A drug history to include over-the-counter drugs, e.g. pseudoephedrine, and prescription drugs like non-steroidal anti-inflammatory drugs, steroids, nasal decongestants, cyclosporine, monoamine oxidase inhibitors, amphetamines and herbal remedies [4].

Basic laboratory investigations include complete blood count, blood chemistry (fasting blood sugar, electrolytes, creatinine), lipid screen (total cholesterol and high-density lipoprotein), urinalysis and an electrocardiogram. If abnormalities are found, further tests may be required. More intense laboratory testing is not cost-effective, and in the absence of clinical evidence, the yield for secondary hypertension is small. Only 5% [5] to 10% [6] of hypertension is the result of secondary causes. Most of the causes of secondary hypertension in the younger adult are relatively uncommon in the elderly with the exception of renal artery stenosis. Other causes of secondary hypertension increases with age mainly owing to the use of drugs such as NSAIDs, the presence of kidney disease, obstructive sleep apnoea and renal artery stenosis [7]. Elderly patients with higher risk of secondary hypertension include those with evidence of diffuse atherosclerosis. An abdominal bruit over one or both renal arteries with other manifestations of vascular disease suggests renal artery stenosis. Renal artery stenosis is uncommon as a cause of hypertension and may present as accelerated, refractory hypertension, sudden unexplained pulmonary oedema or secondary to use of ACE inhibitors with worsening of renal failure.

A national consensus group, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [8], designated three stages (Stages I–III) in place of the earlier designation mild, moderate and severe. In Stage I, the systolic pressure is 140–159 and diastolic 90–99 mmHg, in Stage II the systolic pressure is 160–179 and diastolic 100–109 mmHg, and in Stage III, the systolic pressure is >180 and diastolic >110 mmHg. When systolic and diastolic pressures fall in different categories, the higher should be taken.

Evaluation of target organ damage begins with a physical examination. A thorough examination of the cardiovascular system includes a search for diminished or absent peripheral pulses, abdominal palpation for pulsatile mass and auscultation for abdominal or renal bruits and for evidence of heart failure. Fundoscopic examination may reveal systemic vascular changes. Hypertensive retinopathy together with left ventricular hypertrophy and renal impairment are considered as an indicator of target organ damage [9]. Hypertensive retinopathy develops from arteriolar changes such as tortuosity of blood vessels, arteriovenous nipping and increased light reflex of the arterioles in the initial stages followed by focal or generalised

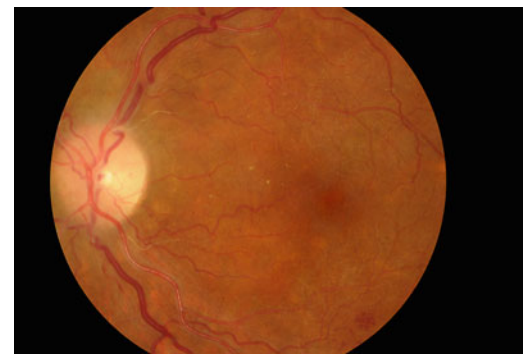


Fig. 1 Hypertensive encephalopathy. Shows few scattered haemorrhages. Silver wiring of superior and inferior temporal arteries. Multiple A/V nipping especially where the superior temporal artery crosses the vein at two points. There are multiple small arteries as ghost vessels and disc swelling showing blurring of the nasal disc margin (Reproduced, with kind permission, from Dr. P. Nithianandan)

retinal arteriolar constriction (Fig. 1). As the disease progresses, haemorrhages (flame-shaped) and small white superficial foci of retinal ischaemia (cotton wool) and later hard yellow exudates arise deep in the retina due to lipid deposition from leaking retinal vessels. The optic disc becomes congested and oedematous in severe hypertension [9]. Studies have indicated a close correlation between degree of blood pressure elevation and severity of kidney dysfunction [10]. In the elderly, elevated blood pressure and ageing give rise to nephrosclerosis resulting in increase in intrarenal vascular resistance, diminished renal blood flow, decrease in glomerular filtration rate and inability to concentrate urine. A chest X-ray and an electrocardiogram look for left ventricular hypertrophy, left atrial abnormality and arrhythmias. Urine analysis should routinely be performed.

In order to determine the overall risk profile for each patient and the need for drug therapy, the Joint National Committee [8] further recognised the need to consider other cardiovascular risk factors (Box 1), target organ damage (Box 2) and co-existing cardiovascular and other clinical conditions. The JNC 6 [8] includes a classification of blood pressure stages and a new risk stratification. It recognises three risk categories of increasing severity (A, B and C) based on the determinants, namely, the cardiovascular risk factors, target organ damage and associated clinical conditions (Table 1). Combining the risk categories with stage of hypertension provides a rational guide to the urgency of therapy.

Box 1 Cardiovascular Risk Factors

Cigarette smoking
Hypercholesterolaemia
ECG evidence of left ventricular hypertrophy
Obesity
Diabetes
Physical inactivity
Family history
Race and ethnicity
Male gender
Advancing years

Box 2 Target Organ Disease

Left ventricular hypertrophy with remodelling
Retinopathy
Nephrosclerosis with proteinuria/renal insufficiency
Congestive heart failure
Stroke
Peripheral vascular disease

Table 1 Risk categories [8]

Risk group A (no additional risk): no cardiovascular risk factors, no clinical cardiovascular disease or target organ damage
Risk group B (moderate additional risk): at least one risk factor not including diabetes, clinical cardiovascular disease or target organ damage
Risk group C (marked additional risk): clinical cardiovascular disease or target organ disease or diabetes with or without other risk factors

Management of Hypertension

Elderly patients are at high risk for mortality and morbidity for hypertension-related diseases, and the studies show that treatment of hypertension (isolated systolic and systolic/diastolic) in the elderly is extremely effective [11, 12]. The general practitioner is best suited to identify, evaluate, manage and control hypertension. He or she should record the blood pressure at each patient encounter.

There have been several randomised controlled treatment trials in elderly patients with systolic/diastolic hypertension [13, 14]. Hypertension Optimal Treatment (HOT) trial reported a decline in "expected" cardiovascular events [15]. The European Working Party on High Blood Pressure in the Elderly trial randomised treatment or placebo in 840 patients over the age with both systolic and diastolic hypertension. Seventy-five percent of the patients were women. After a 12-year follow-up, there was a decrease in the total mortality rate of 27% (47% for men and 18% for women) [16]. The Hypertension in the Very Elderly Trial (HYVET) study [17] demonstrated that in the very elderly,

lowering the pressure to the level of 150/80 mmHg is beneficial.

Guidelines for the initiation of hypertensive therapy for the 80 years and older are not well defined and should follow the guidelines from the eighth report of the Joint National Committee (JNC 8) on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [18]. There is positive evidence that treating hypertension in the elderly and very elderly provides clinical benefits [12]. Several trials have indicated that lowering the systolic blood pressure (SBP) to less than 140 mmHg as recommended by the prevailing guidelines is not upheld by evidence in the elderly [2, 19] and does not benefit the elderly and the very elderly [12].

There are several international guidelines, the Seventh (2003) and Eight (2013) Reports of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [18, 20], the European Society of Hypertension (ESH) and the European Society of Cardiology(ESC) [21], the Canadian Hypertension Education Program recommendations for the management of hypertension [22] as well as a consensus document issued by the American Heart Association, the American College of Cardiology and the Centers for Disease Control and Prevention (AHA/ACC/CDC) [23]. The JNC 7 advised that the elderly achieve the same targets as the general population [24]. JNC 8 however recommended that for elderly patients, there should be a less vigorous approach to begin treatment in those with systolic blood pressure at 150 mmHg or more and whose diastolic blood pressure levels are 90 mmHg or more and to treat below those levels [18]. Algorithm 1 for the patient presenting with high blood pressure.

Lifestyle Changes

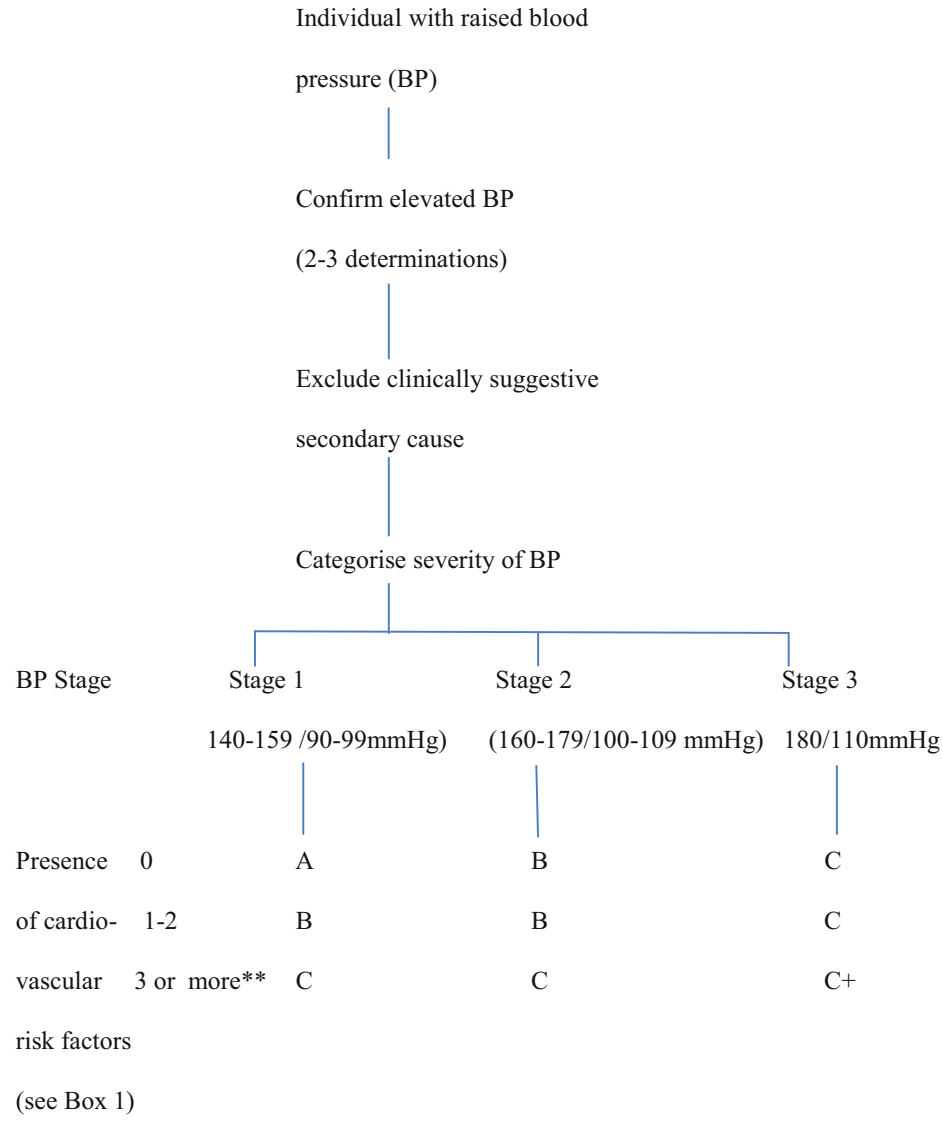
Lifestyle changes to reduce blood pressure include weight reduction, dietary sodium restriction, healthy eating, increase physical activity, moderate alcohol consumption and cease smoking. Obesity is assessed by calculating the body mass index (BMI). BMI = weight (kg)/height squared (m^2), and the normal range is 18.5–24.9 kg/m^2. BMI > 25 represents overweight and BMI > 30 obese. The waist/hip ratio which measures central obesity with upper limits for men is 0.9 and for women 0.8. Data on the effectiveness of lifestyle modification for treatment of hypertension in patients age 60 or over is scanty. Salt intake should be reduced to less than 4 g of salt per day which is approximately 1550 mg of sodium a day [25]. The JNC 7 [20] has recommended sodium intake of 2300 mg/day.

Physical activity such as brisk walking for about half an hour 5 days in the week is to be encouraged. Alcohol consumption to be restricted to two drinks for males and one for women. The diet should be rich in vegetables, fruits and low-fat dairy products.

Drug Treatment

A meta-analysis of treatment of hypertension in older persons (most of them were 60–79 years of age) demonstrated clearly that drug therapy decreased risk of stroke by an average of 32% [26]. The Hypertension in the Very Elderly Trial (HYVET) was a randomised, double-blind placebo-controlled study involving patients aged 80 or older. The results showed that lowering blood pressure of elderly patients could cut their total mortality by one-fifth and their rate of cardiovascular events by one-third [11]. Drugs from any of the main classes are suitable for initiation and maintenance of antihypertensive therapy. The choice of the drug will be dependent on:

(i) The presence of certain conditions, e.g. diabetes with nephropathy, congestive heart failure, post-myocardial, infarction, that should be given appropriate drug [3].
(ii) The presence of co-existing conditions which may influence choice of drug. Antihypertensive medications may have unfavourable or favourable effects in co-existing conditions, for example, elderly patients with urinary incontinence diuretics may affect bladder



Algorithm 1 Patient with High Blood Pressure ** together with Target Organ Damage (see Box 2) and Associated Clinical Conditions. A = low risk; B = moderate risk; C = high risk; C + very high risk Information sources: JNC [8])

control, beta-blockers may have an unfavourable effect in patients with severe peripheral vascular disease and diuretics in gout. ACE inhibitors have a favourable effect in patients with diabetics with microalbuminuria and in those with non-diabetic nephropathy [8].

(iii) The patient's cardiovascular risk profile and the presence of target organ damage.

Clinical trials have indicated that there is no age limit and appropriate antihypertensive therapy should not be withheld because of age [1]. Diuretics and beta-blockers have been suggested as primary therapy for uncomplicated hypertension and other agents for specific situations, for example, in diabetes mellitus or heart failure, ACE inhibitor or A-II receptor blocker (plus a diuretic) [18] (Fig. 2). In an MRC trial on

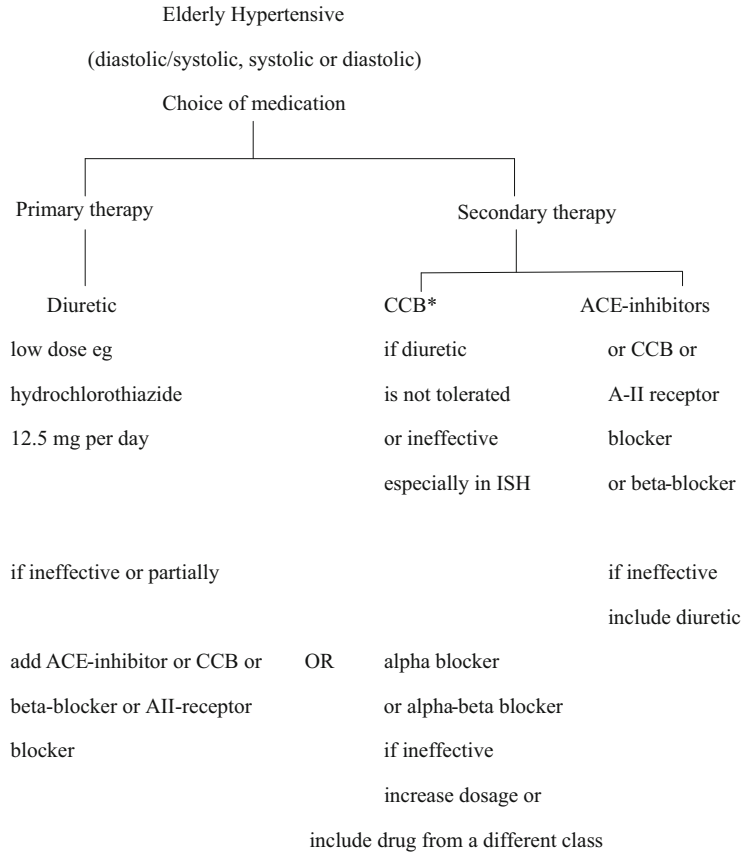


Fig. 2 Drug treatment of hypertension (**CCB* calcium channel blocker) (Information sources: Moser [27])

old adults with hypertension, beta-blockers were poorly tolerated compared with diuretics, and many patients withdrew due to major adverse effects with beta-blockers [28]. In a meta-analysis of ten randomised trials using diuretics and or beta-blockers, two-thirds on diuretic monotherapy were well controlled compared to less than one-third on beta-blocker monotherapy [29]. Thus beta-blockers as first-line therapy of uncomplicated hypertension in the elderly remain unresolved [30]. Calcium channel blockers or ACE inhibitors and angiotensin receptor blockers are more usually used as second-line choice [1] when other agents are contraindicated. Adjunct treatment with nitric oxide (NO) and NO donors is being used because of their effect on large conduit arteries for they reduce systolic blood pressure more than diastolic blood pressure [1, 31]. Spironolactone may reduce arterial stiffness and may be used in resistant ISH [31]. Renin inhibitors represent an alternate strategy, and they lower the blood pressure by effective blockade of the renin-angiotensin system. Aliskiren is the first renin inhibitor, and renin inhibitors can be used in combination with other hypotensives with no appreciable increase in adverse events [30].

Idiopathic systolic hypertension (ISH) is characterised by reduced arterial compliance; calcium channel blockers tends to induce arterial dilatation and hence would be more appropriate as a first-line choice [32]. Elderly patients with ISH should be treated even if they are 80 years or over. In the very elderly, lowering of the blood pressure to the level of 150/80 mmHg is beneficial as shown by the HYVET study [17]. In the elderly,

the blood pressure should be reduced by gradual titration and more so the need to "start low and go slow" and applies equally to combination therapy. Hypertension requires lifelong care and follow-up. The general practitioner should decide how often to follow up depending on the severity, variability of the blood pressure, complexity of the treatment regimes, patient compliance and need for non-pharmacological advice [32]. According to the British Hypertension Society, the follow-up of hypertension is every 3–6 months and should not exceed 6 months [33].

Regardless of lifestyle changes and drug treatment, achieving blood pressure goals often poses a difficult problem. Resistant hypertension has been characterised by the blood pressure remaining above the target levels despite adherence to three antihypertensive agents one of which is a diuretic [34]. An encouraging recourse is renal sympathetic denervation. Several renal sympathetic denervation devices are being developed. Presently it is indicated for patients who satisfy the above criteria and whose systolic blood pressure is greater or equal to 160 mmHg and in the case of type 2 diabetics whose blood pressure is more than or equal to 150 mmHg [35, 36]. The Simplicity HTN-2 trial at the end of 6 months demonstrated that the renal function remained stable, there are no significant procedure related complications and the blood pressure was reduced by 32/12 mmHg [36]. However, the investigators of the Simplicity HTN-3 trial, a blinded trial of sympathetic denervation, failed to show significant reduction of systolic blood pressure in patients with resistant hypertension after renal denervation as compared with a sham control [37].

Low-dose aspirin has been recommended for primary prevention in people over the age of 50 years and for secondary prevention of ischaemic cardiovascular disease [33]. Irrespective of the level of blood cholesterol or LDL, statins have also been recommended for all people with high blood pressure with cardiovascular disease and for primary prevention in people with high blood pressure who have a 10-year risk of cardiovascular disease of >20% [33].

Impact

Buford [38] highlighted the multifaceted risks of hypertension among older adults. Apart from the cardiovascular risks, there are a number of collateral risks in late-life hypertension, for example, dementia, physical disability, presence of postural hypotension and falls. Hypertension has been considered a "silent killer" [39, 40] for it can remain asymptomatic for years before an adverse event occurs [321]. Hypertension treatment may contribute to poor compliance with treatment [321] and impairment of quality of life [41] although the Systolic Hypertension in the Elderly Program (SHEP), Systolic Hypertension in Europe (Syst-Eur) and Study on Cognition and Prognosis in the Elderly (ScOPE) have shown that antihypertensive treatment had no negative impact on quality of life [41]. The negative effect of antihypertensive drugs has to be looked at in reference to the quality of life in the management of hypertension in the elderly, the deterioration of which may result in poor compliance [41]. Because of the high prevalence of co-morbidities in elderly hypertensive patients, clinicians should take into account the co-morbid conditions in their management of hypertension [42, 43]. In the elderly, cognitive function, physical activity, sexual function, symptomatic well-being [41], sleep and social participation are some of the domains that should be looked at in patients receiving antihypertensive therapy [44] (Box 3).

Box 3 Key Points: Hypertension

In patients with sporadically elevated blood pressure or white coat hypertension, a 24-h ambulatory BP monitoring is useful (normal ambulatory blood pressure but with elevated reading in the clinic) [2].

Due consideration should be given to identify any additional cardiovascular risk factors [3] and an overall estimate of cardiovascular risk and furthermore to ascertain target organ damage [3].

(*continued*)

Box 3 Key Points: Hypertension (continued)

Treatment of hypertension (isolated systolic and systolic/diastolic) in the elderly is extremely effective [11, 12]. Isolated systolic hypertension is the most common form of hypertension in the elderly.

In order to determine the overall risk profile for each patient and the need for drug therapy, the Joint National Committee [8] further recognised the need to consider other cardiovascular risk factors, target organ damage and co-existing cardiovascular and other clinical conditions.

Lifestyle changes to reduce blood pressure include weight reduction, dietary sodium restriction, healthy eating, increase physical activity, moderate alcohol consumption and cease smoking.

The JNC 7 [20] has recommended sodium intake of 2300 mg/day.

Idiopathic systolic hypertension (ISH) is characterised by reduced arterial compliance; calcium channel blockers tends to induce arterial dilatation and hence would be more appropriate as a first-line choice [32].

According to the British Hypertension Society, the follow-up of hypertension is every 3–6 months and should not exceed 6 months [33].

Multiple Choice Questions

1. Each of the following regarding hypertension in the elderly is true, EXCEPT:
   A. Nearly two-thirds of those above 75 years have uncontrolled hypertension.
   B. Isolated systolic hypertension is the most common form of hypertension in the elderly.
   C. Hypertension is not a major factor in the development of cardiac failure.
   D. Elderly patients are at high risk for morbidity and mortality for hypertension-related diseases.
2. Each of the following statement regarding diagnosis of hypertension in the elderly is true, EXCEPT:
   A. Measurement of the blood pressure in the elderly should be by correct technique.
   B. Intensive laboratory investigations even in the absence of clinical evidence are cost-effective with regard to secondary hypertension even though the yield is small.
   C. Elderly patients with high risk of secondary hypertension include those with evidence of diffuse atherosclerosis.
   D. Renal artery stenosis may be diagnosed by ultrasound as unilateral small kidney.
3. Each of the following relating to the management of hypertension in the elderly is true, EXCEPT:
   A. Treatment is of no proven beneficial effect in patients above the age of 75 years.
   B. The follow-up of patients with hypertension should be 3–6 months and should not exceed 6 months.
   C. Salt intake should be less than 4 g of salt per day.
   D. Presence of co-existing conditions may influence choice of drug that may have an unfavourable or favourable effect.

MCQ Answers

1 = C; 2 = B; 3 = A

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Peripheral Arterial Disease

7

Contents

Abstract

This review provides an overview of peripheral arterial disease, the prevalence and mechanisms followed by management. The prevalence of symptomatic peripheral arterial disease (PAD) on average is about 5% at around 60 years of age. Atherosclerosis is by far the commonest pathological feature of PAD and accounts for more than 80% of PAD. The clinical manifestations of occlusive PAD are the result of ischaemia of the tissues supplied by the affected arteries and the character of pain related to the severity of the occlusion. The diagnosis in most instances can be confirmed by measuring the ankle-brachial index (ABI). Arterial duplex ultrasound, magnetic resonance angiography, segmental arterial pressure and digital subtraction angiography are useful in locating lesions in PAD. The scientific evidence strongly supports aggressive management of not only symptomatic atherosclerotic disease in terms of lifestyle intervention, lowering blood pressure, lowering lipids and controlling diabetes but also the management of individuals with high multifactorial risks.

Keywords

Peripheral arterial disease · Atherosclerosis · Rest pain · Nocturnal pain · Intermittent claudication · Ankle-brachial index (ABI)

Introduction

The prevalence of symptomatic peripheral arterial disease on average is about 5% at around 60 years of age [1]. The prevalence of asymptomatic

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_6

disease is not generally recognised, and PAD continues to be underdiagnosed and overlooked [2]. It is poorly recognised, and the PARTNERS (Peripheral Arterial Disease Awareness Risk and Treatment: New Resources for Survival) programme revealed that 44% of the cases were diagnosed only after enrolment to the programme [3].

Atherosclerosis is by far the commonest pathological feature of PAD and accounts for more than 80% of PAD in the United States [4]. About 80–90% of the symptoms of PAD are from the femoral and popliteal arteries and 40–50% from tibial and peroneal and 30% from the aortoiliac arteries [4]. A number of etiological factors such as atherosclerosis, age, hypertension, degenerative disease, trauma, infection and inflammatory disorders give rise to PAD. However atherosclerosis is by far the commonest cause, including both occlusive and aneurysmal disease. The risk factors are shown in Box 1.

Box 1 Risk Factors of PAD

Advanced age 70 years or older
Hypertension
Dyslipidaemia
Smoking
Diabetes mellitus
Obesity
Hyperhomocysteinaemia
Known association with coronary heart disease, carotid artery disease and renal artery stenosis

Information sources: Gey et al. [2], Hernando andConejero [5] and Arnow [6]

Clinical Manifestations

The clinical manifestations of occlusive PAD are the result of ischaemia of the tissues supplied by the affected arteries and the character of pain related to the severity of the occlusion. In mild cases the patient may be asymptomatic, and peripheral arterial examination may be nearly normal. Intermittent claudication is the hallmark of occlusive PAD and is characterised by pain on exertion relieved by rest or with dependent position within minutes. With greater occlusion the pain is often felt at night (nocturnal pain), and finally pain is at rest when the stenosis is more than 90%. Depending on the affected arteries, the pain may be felt in the calf, thigh or buttock (Box 2). Ischaemic ulceration occurs following trauma on the toes, foot or heel. It is painful, and the ulcer has a discrete edge and pale base or may be covered with an eschar. In PAD apart from arterial obstruction and limitation of blood flow, there are adverse consequences in the distal skeletal muscles [7] and mitochondrial dysfunction leading to functional impairment [8].

Box 2 Symptoms and Signs According to Location

Iliofemoral occlusive disease:

Diminished pulses throughout unilateral leg buttock claudication may be present

Femoropopliteal occlusive disease:

Normal pulses in inguinal region, thigh and calf claudication

Aortoiliac occlusive disease (Leriche syndrome):

Pulses diminished bilaterally, impotence slow wound healing

Diagnosis

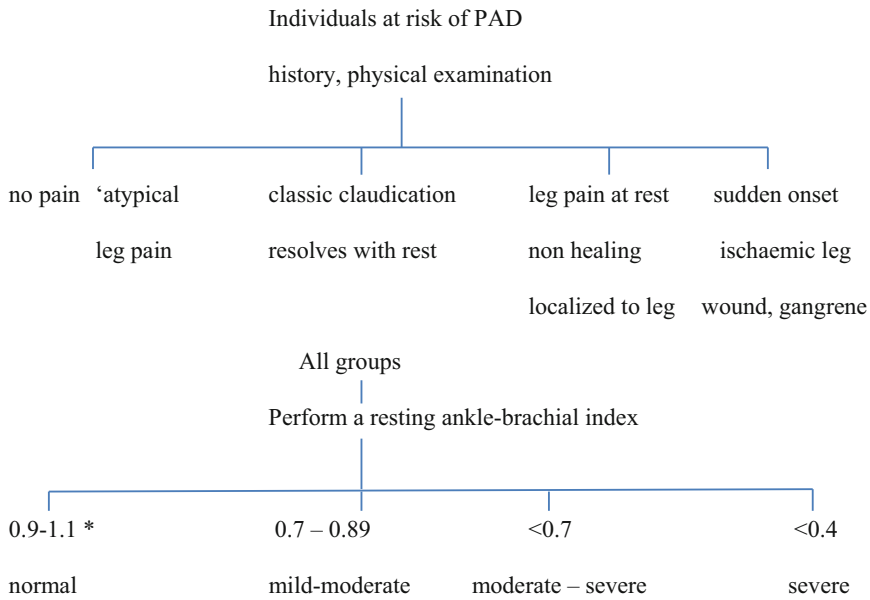
Physical Examination

Includes a (a) vascular examination for integrity of the pulses and presence of bruit and (b) local signs of peripheral arterial disease:

(i) The blood pressure is measured in both arms to note if there is interim asymmetry.
(ii) The peripheral arteries, the radial, brachial, femoral, popliteal, dorsalis pedis and posterior tibial, are palpated.
(iii) The carotid arteries are palpated and auscultated for the presence of bruit.
(iv) The abdomen is palpated and auscultated for the presence of aortic pulsations and bruit.
(v) Auscultation of the abdomen and flanks for bruits.
(vi) Auscultation of the femoral arteries for bruits.
(vii) To look for local signs of PAD
Skin changes (dry, scaly, atrophic), temperature, skin integrity (fissures, ulcerations), toe nails (dystrophic, brittle), hair loss and colour changes with change in position, pallor on leg elevation >1 min, the colour returning within 15 s in mild cases and delayed >40 s suggestive of severe ischaemia. The diagnosis in most instances can be confirmed by measuring the ankle-brachial index(ABI) [9]. The ABI is simple and useful bedside tool for not only confirming the diagnosis but also measuring the severity of the symptomatic PAD and also allows for identification of asymptomatic PAD [10]. Arterial duplex ultrasound, magnetic resonance angiography, segmental arterial pressure and digital subtraction angiography are useful in locating lesions in PAD [2]. An Algorithm 1 is provided for the diagnosis of PAD.

Management

The scientific evidence strongly supports aggressive management [2] of not only symptomatic atherosclerotic disease in terms of lifestyle intervention, lowering blood pressure, lowering lipids and controlling diabetes but also the management of individuals with high multifactorial risks [6, 12, 13] (Box 3). It is



Algorithm 1 For the diagnosis of PAD

possible some relief can occur with modification of risk factors such as cessation of smoking, exercise [6] and pharmacotherapy [2, 12]. The efficacy of vasodilators is questionable. Beta-blockers cause vasoconstriction and should be avoided. Drugs that reduced platelet activity are beneficial. Clopidogrel, a platelet aggregation inhibitor, is associated with decreased progression of arteriosclerotic disease. Pentoxifylline (Trental) may be effective in patients with intermittent claudication. Statins have been shown to reduce the incidence of intermittent claudication in patients with PAD and hypercholesterolaemia [6]. Exercise programmes and clostazil lengthen exercise time until intermittent claudication develops [14].

Revascularisation may not be necessary in most patients with intermittent claudication [15]. Sympathectomy is generally reserved for patients with inoperable disease, and chemical sympathectomy is the most commonly done. Patients with 'critical limb ischaemia' [4, 16] may be considered for such interventions as stenting, balloon angioplasty and surgical vascularisation [12]. Other indications for interventions are severe intermittent claudication interfering with lifestyle or work and vasculogenic impotence [6].

Box 3 General Measures
Lifestyle goals:

Tobacco cessation
Exercise
Healthy food

Risk factor goals:

Optimise hypertension management (<130/90 mm Hg)
Lipid management total cholesterol <5 mmol/L; LDL calculation <3.0 mmol/L
Overweight/obesity
Body mass index <25 Kg/m^2
Diabetes Hb A1c 6.2–7.5%

Prognosis

PAD is an important predictor of coronary and cerebrovascular risk [10, 17]. In a prospective study of 7,000 patients over the age of 65 years, 18% had reduced ABI (<0.9). In 5 years 24% and 19% with symptomatic and asymptomatic PAD were dead as compared to only 9% of all-cause mortality with normal ABI. After taking into account all risk factors, PAD was associated with a 40% increase in mortality [18].

About 80% of the patients with intermittent claudication remain stable. Those with intermittent claudication that require intervention are of the order of 10–20%, and the risk of limb loss (amputation) at 5 years is 1–2% [1]. Patients with symptomatic PAD have a 10-year accrued survival rate of 38% and a 15-year survival rate of about 22%. PAD is associated with a fourfold increase in the risk of cardiovascular death [10]. The more severe the PAD as measured by ABI, the worse the prognosis [19, 20]. In those with critical leg ischaemia, the annual mortality is 25% [21] (Box 4).

Box 4 Prognosis in Patients with Intermittent Claudication (IC)
IC stable: 80%
IC requiring intervention: 10–12%
Amputation at 5 years: 1–2%
5-year mortality (atherosclerotic cause): 20–30%
Coronary artery disease deaths: 60%
Cerebrovascular deaths: 15%
Lowest ABI values annual mortality: 25%

_Information sources: TASC [1], Leng et al. [19], and Newman et al. [20]

Acute Leg Ischaemia

Acute ischaemia of the leg is common in the elderly. Two important causes of an ischaemic limb are embolism and thrombosis of an atherosclerotic stenosis [22, 23]. Other causes are

trauma [22, 23] ('arterial spasm') and arterial dissection. Iatrogenic dissection of femoral, iliac artery can occur during catheterisation. The diagnosis is often missed [22, 23] or delayed and treated inadequately. The typical presentation is a painful, pulseless, pale and paraesthetic limb which may progress to frank gangrene [24] within 24–48 h. Absent pulse is the hallmark for acute ischaemia and is also useful in locating the occlusion. It differs from chronic occlusion in that there is no a collateral blood supply [23]. Acute venous occlusion can produce a similar picture to that of arterial occlusion but can be differentiated with a Doppler study. An ischaemic leg is commonly mottled, but a large femoral embolus produces a marble white leg [25]. Table 1 shows the differences between embolism and thrombosis.

Impact

PAD is a significant contributor to both the burden and national healthcare costs [9, 26] and expenditure with inpatient care. Treatment increased with age at rates 4.5% and 11.8% for patients aged 65–74 and over 85 years, respectively [27]. PAD coexists with coronary artery disease and other atherosclerotic disorders [28]. PAD and intermittent claudication (IC) increase with age; however the prevalence of PAD is high and that of IC is low in the elderly [29]. An office practice study evaluating PAD revealed that HR-QoL burden is somewhat similar to other types of cardiovascular disease [30]. In PAD patients there is a high prevalence of depression and considerable reduction in the quality of life and this most likely related to the ischaemic symptoms [30] (Box 5).

Table 1 Differences between embolism and thrombosis

	Embolism	Thrombosis
Aetiology	Rheumatic heart, myocardial infarction, atrial myxoma, aneurysms, vegetations	Atherosclerotic stenosis, hyperviscosity states (drug induced), profound dehydration
History	Sudden onset	History of IC, rest pain in either leg
Examination	Full normal pulses in opposite limb suggestive of AF, heart disease	Reduced pulses in opposite limb

Information sources [22, 23]

Box 5 Key Points: Peripheral Arterial Disease (PAD)

Most epidemiological studies report the prevalence of PAD to be about 10–25% in both genders over 55 years [29].

Atherosclerosis is by far the commonest pathological feature of PAD and accounts for more than 80% of PAD in the United States [4].

The diagnosis in most instances can be confirmed by measuring the ankle-brachial index (ABI) [9].

The scientific evidence strongly supports aggressive management [2] of not only symptomatic atherosclerotic disease in terms of lifestyle intervention, lowering blood pressure, lowering lipids and controlling diabetes but also the management of individuals with high multifactorial risks [6, 12, 13].

It is possible some relief can occur with modification of risk factors such as cessation of smoking, exercise [6] and pharmacotherapy [2, 12].

PAD is an important predictor of coronary and cerebrovascular risk [10, 17].

The more severe the PAD as measured by ABI, the worse the prognosis [19, 20].

In those with critical leg ischaemia, the annual mortality is 25% [21].

Acute ischaemia of the leg is common in the elderly. Two important causes of an ischaemic limb are embolism and thrombosis of an atherosclerotic stenosis [22, 23].

Multiple Choice Questions

1. The following is true of peripheral arterial disease (PAD) *except*:
   A. Atherosclerosis is the commonest cause for both occlusive and aneurysmal disease.

B. PAD is an important predictor of coronary and cerebrovascular risk.
C. In femoropopliteal disease buttock claudication is present.
D. PAD is associated with a fourfold risk of cardiovascular death.

2. The following statements regarding peripheral arterial disease (PAD) is true *except*:
   A. Ankle-brachial index (ABI) is a simple and useful tool not only in diagnosis but also to determine severity.
   B. Sympathectomy is generally reserved for patients with inoperable disease.
   C. The efficacy of vasodilators is questionable.
   D. Those with intermittent claudication that require intervention are in the order of 10–25%, and the risk of limb loss (amputation) at 5 years is 30%.

MCQ Answers

1 = C; 2 = D

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Part II

Respiratory Diseases in the Elderly

Part II provides an overview of the common respiratory diseases in the elderly and includes sleep disorders in the elderly. The review will discuss the prevalence and mechanisms and highlight the improvements that have occurred in clinical care. Pneumonia is one of the commonest infections in the elderly. In the elderly the incidence and prevalence is four times that of younger population. The organisms affecting the elderly are the same as in the younger adults but with a different age-related distribution. In the elderly the symptoms and signs are more subtle and misleading. Current approach to empirical management depends on the type of patient (community or hospital) rather than the type of symptoms (typical or atypical). The prevalence of chronic obstructive pulmonary disease (COPD) is strongly associated with age. It will rise from the 12th place to the 5th place in the World Health Organization ranking list of disability-adjusted life years (DALYS). Viral and bacterial infections and air pollution cause exacerbations of COPD and indicate worsening of the underlying chronic inflammation of the airways, and the frequency of the exacerbations is one of the important determinants of health-related quality of life. Asthma is common in the elderly and is often misdiagnosed and or underdiagnosed and undertreated resulting in significant negative consequences for the patients health. In the elderly asthma there are at least two phenotypes, those with long-standing asthma and those with late onset asthma. Between 30% and 45% of all lung cancers are diagnosed in patients older than 70 years. About 40% of pulmonary embolism found at necropsy of old patients were not suspected antemortem. Accurate diagnosis is crucial because if untreated, in-hospital mortality is up to 30% whereas with appropriate treatment it is only 8%. Primary sleep disorders such as obstructive sleep apnoea, periodic limb movement (PLM), restless leg syndrome (RLS), and circadian rhythm disorders together with REM and sleep apnoea syndrome (SAS) are the most common sleep disorders in relatively healthy elderly people.

Pneumonia in Geriatric Patients

8

Contents

Abstract

In the elderly, the incidence and prevalence of pneumonia are four times higher than that of younger population. Age-associated changes are risk factors in the elderly for lower respiratory tract infections. Elderly patients have an excessive incidence of nosocomial pneumonia. The organisms affecting the elderly are the same as in the younger adults but with a different age-related distribution. In the elderly, the presenting features are often determined more by the host than by the specific organism causing the infection. The radiological appearances produced by the different organisms are variable and the radiological patterns are inconclusive, and there is no correlation between the pathological changes and the radiological appearances. The current approach to empirical management dwells on the type of patient (community or hospital) rather than the type of symptoms (typical or atypical). The antibiotic chosen should have an appropriate spectrum of the likely pathogens causing these infections and upon local resistance patterns of suspected organisms. The elderly have higher rates of hospitalization with a significant impact on morbidity and mortality.

Keywords

Nosocomial pneumonia · Community-acquired pneumonia · Pneumococcal vaccine · Pneumonia severity index · Curb-65

Introduction

In the elderly, the incidence and prevalence of pneumonia are four times higher than that of younger population [1]. 17 of 1000 hospital discharges of patients over the age of 70 years had a diagnosis of nosocomial pneumonia, whereas only 2 of 1000 hospital discharges in individuals

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_10

younger than 60 years had the same diagnosis [2]. In the United States, community-acquired pneumonia is the fifth leading cause of death and a common cause of death from infectious diseases in persons aged 65 years and over [3]. Nursing home residents are at high risk of developing pneumonia, and in a study of 1000 nursing home residents, 33 had to be hospitalized per year for treatment of pneumonia [4]. The mortality of patients aged between 80 and 91 years was 38% compared with 7% of persons 30 years or younger [5]. Approximately 20% of nosocomial infections in the elderly are due to pneumonia that is only second to urinary tract infections [6, 7].

The common risk factors are shown in Box 1. Age-associated changes such as decreased clearance of pathogens by reduction of the number of cilia and reduced immune function are risk factors in the elderly for lower respiratory tract infections [8]. Significant risk factors for nosocomial pneumonia in the acute care setting in patients with neurological and renal diseases and deteriorating health included altered level of consciousness, disorientation, dependency for bathing and feeding, aspiration, difficulty with nasopharyngeal secretions and presence of nasogastric tube [8, 9]. Elderly patients have an excessive incidence of nosocomial pneumonia. Community-acquired pneumonia (CAP) and ventilator-associated pneumonia are the second most common nosocomial pneumonias and produce the highest mortality [10]. Some of the risk factors for nursing home residents for developing pneumonia are marked disability, bed-bound status, urinary tract infection, swallowing difficulties, male sex and age [11, 12].

Box 1 Common Risk Factors for Pneumonia in the Elderly
Age over 70 years
Cigarette smoking
Chronic pulmonary airway disease
Co-morbid illness, e.g. congestive heart failure, chronic liver disease, chronic renal failure, diabetes, neoplastic disease
Neurological disorders, e.g. stroke, dementia, neuromuscular diseases
Malnourished, debilitated, bedridden state, frailty
Chronic alcoholism
Immunosuppression, weakened immune systems
Sedation, surgery, tracheal intubation

Information sources: Mandell et al. [13], Koivula et al. [14], Hanson et al. [15] and Fleming et al. [16]

Pneumonia in the elderly may be classified according to the patient's location where the pneumonia was acquired. Pneumonias acquired from the community are termed community-acquired pneumonia (CAP), and those acquired in aged care facilities or nursing homes are termed nursing home-acquired pneumonias (NHAP) and those acquired in hospital as hospital-acquired pneumonias (HAP) (Table 1). Pneumonias have also been classified on the basis of the causative organism. There is no significant distinction in the clinical and radiological presentations between the classical and atypical pneumonias [21] and is of little use clinically. More importantly what is required is a high degree of suspicion for the different organisms and the mode of therapy [22].

The organisms affecting the elderly are the same as in the younger adults but with a different age-related distribution. *S. pneumoniae* is diagnosed most often in both the young and the old; however, *H. influenzae* is relatively more common in the elderly [19]. *H. influenzae* and *Moraxella catarrhalis* are increasingly important in patients with underlying lung disease [23, 24]. *Staphylococcus aureus* pneumonia is usually acquired by aspiration from the upper respiratory tract and occurs in debilitated hospitalized patients. Less frequently, it is a community-acquired pneumonia when it follows influenza. Atypical pneumonias occur in the same rate as in younger adults [25], but mycoplasma is more common in young adults and in contrast

Table 1 Classification according to location of infection

Location	Pathogens
Community-acquired pneumonia (CAP)	
Typical	*Streptococcus pneumoniae*, *Haemophilus influenzae*
	Moraxella catarrhalis, *Oral anaerobes*
	Klebsiella pneumoniae
Atypical	*Viral influenza* *, *Mycoplasma*, *Legionella*
	Chlamydia pneumoniae, *Staphylococcus aureus(only postviral influenza)*
Nursing home-acquired pneumonia (NHAP)	
Streptococcus pneumoniae, *Haemophilus influenzae*	
Moraxella catarrhalis, *Legionella*, *oral anaerobes*	
*Influenza** (*aspiration pneumonias*), *Chlamydia pneumoniae**	
Hospital-acquired pneumonia (HAP) (Nosocomial pneumonia) *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*	
E. coli	
Aerobics, *Gram-negative organisms*	
Acinetobacter, *Legionella*	

Source of information: Schaaf et al. [17], Jones [18], Cunha [19] and Johnson et al. [20]

legionella is more common in the elderly [19] (Table 1).

A great variety of organisms give rise to Gram-negative pneumonias, and the most important in the hospital setting are enterobacteria (*Klebsiella pneumoniae*, *Escherichia coli*), *Haemophilus influenzae and Pseudomonas aeruginosa*. These organisms are the major cause of nosocomial pneumonia and are the major cause of hospital mortality and morbidity. *Klebsiella pneumoniae* is usually nosocomial but occasionally community acquired particularly in chronic alcoholic patients. *Moraxella catarrhalis* typically occurs in the elderly with underlying disease including lung cancer or on steroids. It is relatively a mild pneumonia. *Legionella pneumophila* is among the third or fourth microbial cause of CAP, and these patients are more likely to have severe CAP as characterized by severe abnormal vital signs, more extensive infiltrate on chest X-ray, necessitating admission to intensive care unit [26, 27]. Multiple strains may colonize water distribution systems, but only a few strains will cause disease in patients exposed to the water. Viral pneumonias are unusual in adults (Table 1). In older adults, influenza virus AH3N2 and respiratory syncytial virus are the most commonly singled out viral pathogens [28].

Clinical Manifestations

Organisms pathophysiologically express themselves in a particular pattern which correlates with the signs and symptoms. Bacterial pneumonias usually have an acute onset with fever, chills or rigours, cough, purulent sputum, high temperature, chest pain and leucocytosis with neutrophilia. Mycoplasma and viral pneumonias have subacute onset with upper respiratory symptoms, low pyrexia and scanty sputum, and neutrophilia is absent. However, in the elderly, the presenting features are often determined more by the host than by the specific organism causing the infection [22]. In the elderly, the symptoms and signs are more subtle and misleading. Twenty-five to fifty percent of the patients have no fever, chills or rigours which rarely occur, and symptoms and signs such as cough, sputum and breathlessness may be absent, or the symptoms may be a poor predictor of an infiltrate [22]. Cough and chest pain may be absent in some cases and occur in 20% and 55%, respectively, in the elderly [29] .The presenting feature may be a change in the mental state ranging from confusion to mania or altered sensorium. In fact delirium may be the only manifestation in the elderly [30]. Forty-five percent of

the elderly patients with pneumonia showed delirium compared to 29% in controls [31]. Two other studies reported similar findings with a prevalence of 47% and 15%, respectively, of elderly patients with community-acquired pneumonia at admission [32, 33]. In the elderly, atypical manifestations such as mental confusion, loss of appetite and prostration are frequent [1, 34–36]. Tachycardia and tachypnoea are important clinical features in the elderly and may be the early manifestations [22]. In the elderly, a respiratory rate higher than 24 breaths/minute is the most sensitive sign [29]. Relative bradycardia has been overemphasized as a diagnostic finding in legionellosis but can often be seen in elderly patients with advanced pneumonia. Chest pain has a sensitivity of about 30% [29]. Another presentation is an acute decompensation of an underlying disease, for instance, congestive heart failure, chronic obstructive airway disease and diabetes [37]. Influenza virus and respiratory syncytial virus infections occur during winter months. The former raises the highest suspicion in patients with high fever, myalgias and cough-stained sputum and the latter with coryza, wheeze, low-grade fever and patchy infiltrates and should be considered especially if rapid testing for influenza is negative [28]. Falls are usually a hint that the person is unwell [38].

Legionella spp., *Chlamydia pneumoniae* (now known as *Chlamydophila pneumoniae*) and *Mycoplasma pneumoniae* are important causes of CAP. Legionellosis presents a broad spectrum of illness ranging from low-grade fever and mild cough to stupor, respiratory failure and multiorgan failure. It appears to cause a more severe illness than most common bacterial pathogens associated with CAP. A short prodrome is followed by symptoms typical of bacterial pneumonia and sometimes accompanied by extrapulmonary manifestations (gastrointestinal, renal, neurological and cardiac).

Three species are recognized with *Chlamydia pneumoniae*. The third new species *Chlamydia pneumoniae* (TWAR) is a common cause of pneumonia. The other two that infect humans are *C. psittaci* and *C. trachomatis* [39]. *C. pneumoniae* occurs worldwide and is transmitted from person to person [40]. Infections are mostly mild or asymptomatic but occasional severe pneumonia occurs [40]. It is most common in children and young adults [39, 41] but can cause pneumonia in older adults and persons with chronic diseases [41]. *C. psittaci* causes psittacosis; the manifestations range from mild febrile illness to a severe pneumonia. The infection is derived from budgerigars and parrots.

Mycoplasma occurs in the elderly but is more common in young adults. The diagnosis caused by *Legionella* spp., *Mycoplasma pneumoniae* and *C. pneumoniae* has been implied by PCR on a single throat swab specimen and is specific, rapid and sensitive [42]. Other laboratory tests for *Legionella* include direct fluorescent antibody and culture [42] and urinary antigen test [43]. Anaerobic pneumonias may be acute but more often subacute or chronic. There is a history of aspiration or altered sensorium and almost invariably periodontal disease. A variety of bacteria are implicated, microaerophilic *Streptococcus*, *Bacteroides* and *Fusobacterium*.

Radiological Findings

The radiological appearances produced by the different organisms are variable and the radiological patterns are inconclusive, and there is no correlation between the pathological changes and the radiological appearances. In *Streptococcus pneumoniae*, the changes are homogenous, non-segmental consolidation. *Staphylococcus aureus* classically shows multilobar shadowing, early effusion, cavitation, pneumatocele formation and spontaneous pneumothorax [44]. In Gram-negative pneumonias, the bases are predominantly affected; *Klebsiella* may resemble *S. pneumoniae*. In *Legionella pneumophila* a peripheral lower-zone consolidation, less commonly cavitation, may be seen. About 40% of the patients in a study combining clinical and radiological findings had three patterns suggestive of Legionnaire's, rapidly progressive pneumonia, lobar opacity and multiple peripheral opacities [45]. In *Chlamydia pneumoniae*, alveolar opacities (65%) and predominantly unilateral in distribution and small effusions and may progress to bilateral mixed interstitial and alveolar changes [46]. *Anaerobic* pneumonias may show

consolidation in the segments involved – apical lower, posterior upper or posterobasal – and without treatment cavitation, lung abscess and empyema may occur [47].

Management

Preventive Measures

Pneumococcal disease in the elderly causes considerable mortality and morbidity and hence underscores the need for prevention. In the United States, 10,000–40,000 die each year due to influenza and its complications, and approximately 80% of these deaths are among the elderly [48]. Vaccination against pneumococcal infection and influenza is currently recommended for all persons 65 years and over and has been shown to be beneficial in preventing pneumonia in the elderly [49–52].

Risks for pneumococcal invasive disease (PID) include the young; the old, affecting those with co-morbidities (such as chronic renal failure, chronic heart and lung disease, immunodeficiency); crowded environments; and poor socioeconomic conditions [53]. The 23-valent polysaccharide pneumococcal vaccine is currently recommended [54]. There is still no convincing evidence regarding the efficacy of pneumococcal vaccine against pneumococcal pneumonia in the elderly population [55]. However, the efficacy of pneumococcal vaccine in the prevention of PID such as bacteraemia which is the main complication in pneumonia has been demonstrated [54]. Influenza vaccine reduces the risks for pneumonia, hospitalization and death in elderly persons during an influenza epidemic if the vaccine strain is identical or similar to the epidemic strain [52].

Treatment

Factors such as location where the infection was acquired, the tempo of the disease course and laboratory and radiological findings are not helpful in determining the causative agent [56]. The initial antibiotic therapy for the elderly patient with pneumonia should therefore be empirical, based on known guidelines [56]. Current approach to empirical management dwells on the type of patient (community or hospital) rather than the type of symptoms (typical or atypical) [20]. The antibiotic chosen should have an appropriate spectrum of the likely pathogens causing these infections [57] and upon local resistance patterns of suspected organisms [15, 57]. Because of the difficulty in determining the infective organism, stratification by severity and co-morbidity of the illness is crucial [13]. For estimation of the severity, the Pneumonia Severity Index (PSI) [58] and the CURB-65 (confusion, uraemia, respiratory rate low blood pressure and age 65 years or older) [59] have been validated as useful aids. The Infectious Diseases Society of America and the American Thoracic Society (IDSA/ATS) recommend the use of one or the other for severity assessment in community-acquired pneumonia [60]. PSI is calculated from several clinical and biochemical parameters, whereas the CURB-65 is calculated on five indices and is easier to use. The PSI is commonly used in the United States [58, 61]. Whether PSI can identify low-risk patients who can be safely treated in the community with oral antibiotics is unclear although a high PSI score corroborates with admission to hospital or intensive care unit [61]. The choice of the drug will depend on factors such as antibiotic allergy/tolerance, prior use of the antibiotic and co-morbidity such as renal insufficiency [22]. The Australian guidelines somewhat differ from the international guidelines. IDSA/ATS recommends that CAP management guidelines be locally adapted and implemented [60].

Factors favouring hospitalization are (i) age above 65 years, (ii) co-morbid illnesses (lung disease, cardiac failure, diabetes, renal insufficiency and neoplastic disease), (iii) location where the infection was acquired (community or nursing home), (iv) severity of the illness respiratory rate >30 breaths/min, hypotension, diastolic <60 mmHg, pulse rate <50 bpm or >140 bpm, cyanosis, extremes of temperature 38.3 °C or hypothermia, widespread involvement on auscultation and mental confusion), (v) poor home circumstances, (vi) probability of high-risk aetiology (pneumonia following influenza illness in the elderly) (staphylococcal) and (vii) hospitalization

required for diagnosis or therapy [34–36, 58, 60] (Tables 2 and 3).

Impact

Prevalence of pneumonia increases with age as does the mortality, and it is envisaged that the medical and economic impact of the disease will increase [3]. The elderly have higher rates of hospitalization with a significant impact on morbidity and mortality. The calculated annual cost of treating patients aged 65 years and over with pneumonia is $4.8 billion compared to $3.6 billion for aged below 65 years [66]. The average hospital stay was 7.8 days for the older person and 5.8 days for a younger, and the costs were $7166 and $ 6042, respectively [66]. At 24 months following pneumonia, functional status

Table 2 Some antibiotics used in pneumonia

I. Beta-lactam antibiotics
(i) Penicillins – e.g. (a) broad spectrum, amoxicillin plus clavulanic acid and (b) extended spectrum, piperacillin, ticarcillin, carbenicillin
(ii) Cephalosporins – e.g. (a) third generation, ceftriaxone (1–2 g daily), cefotaxime (1–2 g every 8 h), with antipseudomona activity, ceftazidime. (b) Fourth generation, e.g. cefepime, cefpirome (enhanced activity against Gram-positive bacteria)
(iii) Carbapenems – imipenem, ertapenem (ig IV), meropenem, doripenem
(iv) Beta-lactamase inhibitors – clavulanic acid, sulbactam, tazobactam
(v) Monobactam, e.g. aztreonam
II. Macrolides – erythromycin, roxithromycin, clarithromycin (500 g bd; – XL 2 × 500 mg daily), azithromycin (500 mg daily orally or IV)
III. Quinolones – third generation: spirofloxacin, levofloxacin (750 mg daily), moxifloxacin (400 mg daily)

Sources of information: Macrolide Antibiotics [62], Australian Medicines Handbook [63], File [64] and American Thoracic Society [65]

Table 3 Empirical treatment according to setting

I. Community-acquired pneumonia (CAP)
I. Home (outpatient)
(a) Mild to moderate without co-morbid illness
Macrolide
Doxycycline (weakly recommended)
Alternately amoxicillin +– doxycycline or roxithromycin or clarithromycin
(b) Mild to moderate with co-morbid illness
Fluoroquinolone (moxifloxacin, gemifloxacin or levofloxacin) or beta-lactam + macrolide
Alternately amoxicillin +– doxycycline or macrolide
I. Hospital-acquired pneumonia (nosocomial pneumonia)
(a) Combination therapy required (in general medical ward) aminoglycoside or fluoroquinolone + ticarcillin or piperacillin + beta-lactam blocker or fluoroquinolone (e.g. levofloxacin, moxifloxacin) or a combination of macrolide + beta-lactam
(b) Intensive care unit (very severely ill)
(i) Pseudomonas likely: antipseudomonal beta-lactam (piperacillin-tazobactam, impipenem, meropenem) + fluoroquinolone (e.g. ciprofloxacin or high-dose levofloxacin) or aminoglycoside or macrolide
[a]Macrolide with either antipseudomonal beta-lactam + gentamicin or ciproxin + gentamicin
(ii) Pseudomonas unlikely: third generation cephalosporin + macrolide (IV azithromycin) or fluoroquinolone
Third generation cephalosporin + macrolide or IV penicillin + gentamicin + azithromycin

[a]Overuse of fluoroquinolones as a single agent may promote quinolone resistance, Neralla and Meyer [8], [55]
[b]Macrolides and the fluoroquinolones can prolong QT interval, and the elderly may be also susceptible to drug-associated QT interval prolongation, File [64], [66]
Information sources: Bodmann [57], Mandell et al. [60], American Thoracic Society [65] and File [64]

was the main factor for survival, and according to Muder [12], the mortality scores for the varied activities of daily living scores were as follows: score 10 = 48% mortality, score 11–15 = 75% and score 16 = 77% (Box 2 and 3).

Box 2 Key Points: Pneumonia in the Elderly (Clinical Expression)

In the elderly, the incidence and prevalence are four times higher than that of younger population [1].

It is a leading cause of mortality [3] and morbidity and higher rates of hospitalization in the elderly [4].

In the elderly, the presenting features are often determined more by the host than by the specific organism causing the infection [22].

In the elderly, the symptoms and signs are more subtle and misleading. Twenty-five to fifty percent of patients have no fever, chills or rigours which rarely occur, and symptoms and signs such as cough, sputum and breathlessness may be absent, or the symptoms may be a poor predictor of an infiltrate [22].

The organisms affecting the elderly are the same as in the younger adults but with a different age-related distribution. *S. pneumoniae* is diagnosed most often in both the young and the old; however, *H. influenzae* is relatively more common in the elderly [19].

Box 3 Key Points: Pneumonia Treatment

The initial antibiotic therapy for the elderly patient with pneumonia should therefore be empirical based on known guidelines [53].

The antibiotic chosen should have an appropriate spectrum of the likely pathogens causing these infections [54] and upon local resistance patterns of suspected organisms [13, 54].

Because of the difficulty in determining the infective organism, stratification by severity and co-morbidity of the illness is crucial [18].

The choice of the drug will depend on factors such as antibiotic allergy/tolerance, prior use of the antibiotic and co-morbidity such as renal insufficiency [25].

However, the efficacy of pneumococcal vaccine in the prevention of PID such as bacteraemia which is the main complication in pneumonia has been demonstrated [51].

Influenza vaccine reduces the risks for pneumonia, hospitalization and death in elderly persons during an influenza epidemic if the vaccine strain is identical or similar to the epidemic strain [49].

Multiple Choice Questions

1. The following relating to pneumonia in the elderly are true, except:
   A. *H. influenzae* is more common in the elderly compared to the young.
   B. In the elderly, the signs and symptoms are different from the young.
   C. *Moraxella catarrhalis* typically occurs in the elderly with underlying lung disease including lung cancer or on steroids.
   D. Viral pneumonias are usual in adults.
2. The following relating to pneumonia in the elderly are true, except:
   A. In the elderly, the presenting features are often determined by the specific organism carrying the infection than by the host.
   B. There is convincing evidence regarding the efficacy of pneumococcal vaccine against pneumococcal pneumonia in the elderly population.
   C. The presenting features in the elderly may be a change in the mental state ranging from mania to confusion.
   D. Risk of pneumococcal invasive disease (PID) includes the old, co-morbidities, poor socio-economic and environmental factors.

MCQ Answers

1 = D; 2 = B

Case Study of a Patient with Delayed Resolution of Pneumonia/Missed Diagnosis

Presentation: A 75-year-old man was admitted to the hospital with cough, yellow sputum and fever with chills over the past 4–5 days. He had no haemoptysis. He was a smoker for several years. Examination revealed a temperature of 38.8°C. There was little in the way of signs in the lungs. X-ray of the chest showed – see Fig. 1. He was treated with IV ceftriaxone. His symptoms subsided to a large extent and a repeat X-ray done 10 days later showed – see Fig. 2. A closer look at the earlier X-ray revealed erosion of the second, third and fourth ribs abutting the lung shadow. In view of this finding, a CT scan was done which confirmed the bone involvement (Fig. 3).

Comment: Factors for treatment failure or delayed resolution of pneumonia include antibiotic-resistant pathogen, cavitation, pleural effusion, cardiac failure, wrong choice of antibiotics and neoplasia. Routine follow-up chest X-rays for patients who are responding clinically are unnecessary unless symptoms and signs persist or at higher risk of underlying malignancy [67]. The clinical features of bronchoalveolar carcinoma resemble that of pneumonia, and malignant obstruction often masquerades as viral pneumonia, segmental atelectasis or pneumonitis [68].

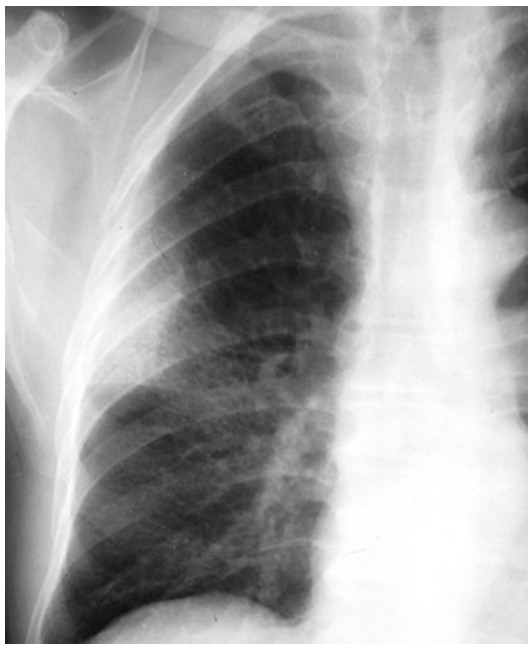

Fig. 1 Shows a wedged –shaped opacity in the right midzone suggestive of pneumonic consolidation

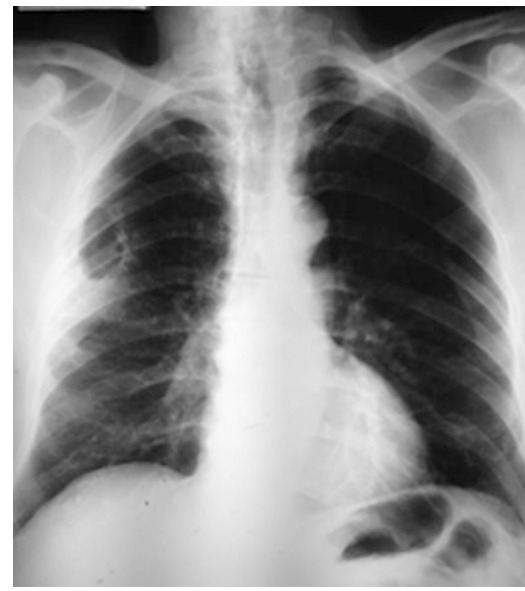

Fig. 2 The lesion shows cavitation and erosion of the 2nd, 3rd and 4th ribs abutting the lung opacity

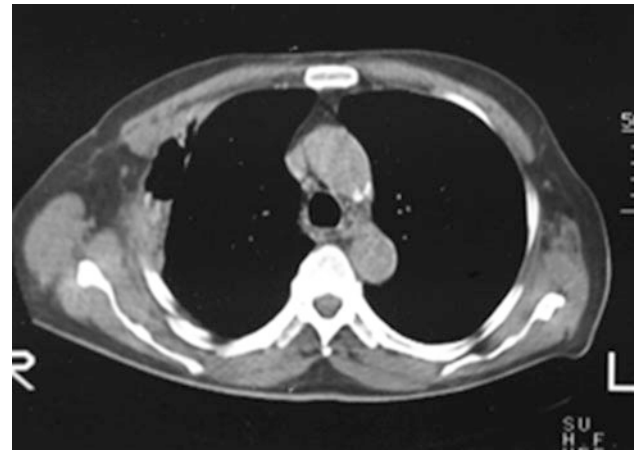

Fig. 3 CT scan showing the same changes as in Fig. 2

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Chronic Obstructive Pulmonary Disease (COPD)

9

Contents

Abstract

The prevalence of COPD is strongly associated with age. It will rise from the 12th place to the 5th place in the World Health Organisation ranking list of disability-adjusted life years (DALYS). COPD is one of the leading causes of morbidity and mortality in the industrialised and developing countries. Ageing of the population and past smoking are the major causes of the increase in COPD. The common risk factors associated with non-smoking COPD are air pollution and occupational exposures to fumes and dust. Airflow limitation is generally progressive with COPD; however, the rate of decline is highly variable. Historically COPD has been categorised into two clinical phenotypes, 'pink puffer' and 'blue bloater'. Spirometry is the most useful measure of outflow obstruction. Viral and bacterial infections and air pollution cause exacerbations of COPD and indicate worsening of the underlying chronic inflammation of the airways, and the frequency of the exacerbations is one of the important determinants of health-related quality of life.

Keywords

COPD · Airway remodelling · Spirometry · Long-acting beta-2 agents (LABAs) · Oxygen therapy · Acute exacerbation

Introduction

The prevalence of COPD continues to increase with changes in the size and composition of the population; the prevalence increases from

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_13

21/1000 in 1994 to 33/1000 in 2015 for men and 10/1000–23/1000 for women [1]. It will rise from the 12th place to the 5th place in the World Health Organisation ranking list of disability-adjusted life years (DALYS) by 2020 [1]. Its prevalence is strongly associated with age, and data from a general population revealed the prevalence of chronic bronchitis and emphysema increases with age in both genders [2]. The prevalence in those over 65 years was fourfold compared to the 45–64-year-old group [3, 4]. The prevalence worldwide is likely to be underestimated as COPD lacks precise definition, represents several different disease processes [5] and lacks age-adjusted estimates [6]. COPD is one of the leading causes of morbidity and mortality in the industrialised and developing countries [2], and its prevalence and mortality are still increasing in response to increasing smoking [5]. Because of the rising incidence of COPD, its significant mortality and morbidity rates and its substantial pragmatic and functional implications worldwide will impose a heavy economic burden on individuals and state.

There are several causative or risk factors involved in COPD. The major causative factor is cigarette smoking, but inhalational exposure to other irritants and genetic factors is also important. Ageing of the population and past smoking are the major causes of the increase in COPD [1]. In cigarette smokers susceptible to COPD, the rate of decline as measured by the FEV_1 is three- to fivefold compared to age-related rate. The Lung Health Study had shown that over the 11-year study, the rate of FEV_1 decline in the sustained non-smokers slowed to 30 ml/year in men and 22 ml/year in women compared to 66 ml/year and 54 ml/year decline in continuing smokers, respectively [7]. Active smoking causes both mucous secretion and airway obstruction. Mortality is related to the amount of cigarettes smoked [8]. In air pollution, sulphur dioxide and particulates are associated with chronic simple bronchitis and COPD [9]. Direct and indirect airway hyperresponsiveness improved with 1-year cessation of smoking but without noteworthy changes in lung function and sputum inflammation [10]. Smokers with a family history of airways obstructive disease are more likely to develop COPD.

Physical Signs

The typical patient develops a large barrel chest and uses accessory muscles on respiration with costal margin retraction on respiration. The breath sounds are diminished and the heart sounds distant. Expiration is prolonged with generalised wheezing predominantly on expiration. Historically COPD has been categorised into two clinical phenotypes, 'pink puffer' and 'blue bloater'. The 'blue bloater' type of COPD may also have cyanosis at rest or on mild exertion, ankle oedema [11], crackles at lung bases and loud P2 (difficult to hear in COPD). The 'pink puffer" may also have expiratory pursed-lip breathing (auto-PEEP), thin body build and tendency to lean forward over a support to assist breathing [9]. In the blue bloater, the main underlying pathology is chronic bronchitis, whereas in the pink puffer, it is emphysema [11]. In the former there is excessive mucus production with airway obstruction, whereas in the latter, there is destruction of the pulmonary capillary bed and reduced ability to oxygenate blood resulting in compensatory hyperventilation and have less hypoxaemia and hence 'pink puffer'. The patient is older with skeletal muscle wasting [11]. In the case of the 'blue bloater', the increased obstruction results in decreased ventilation, leading to hypoxaemia and hypercapnia [11], and usually presents with congestive heart failure [12].

Diagnosis

The diagnosis of COPD is suggested by a history of smoking and shortness of breath over several years, a productive cough and clinical signs of airway obstruction. Spirometry is the most useful measure of outflow obstruction [7]. It is indispensable in establishing the diagnosis because it is a standardised and reproducible test that objectively confirms the presence of airflow obstruction. The forced vital capacity (FVC) and forced expiratory

volume in 1 s (FEV_1) are both decreased, but FEV is reduced to a greater degree causing a reduction in the FEV_1/FVC ratio [13, 14]. FVC is initially normal but is reduced as the disease progresses. FEV_1 is the most useful test to assess severity and progress COPD [6], and a decrease in serial testing of FEV_1 is associated with increased mortality [15]. Staging and severity of COPD are as follows: stage 1 FEV_1 >50% predicted, mild; stage II FEV_1 35–49% predicted, moderate; and stage III FEV_1 <35% predicted, severe [1]. Measurement of the diffusing capacity for carbon monoxide (DLCO) is helpful in the context of fixed airflow obstruction; a decreased diffusion capacity indicates loss of alveolar-capillary areas suggesting emphysema.

The early stages of the disease are characterised by acute chest illnesses with increased cough, sputum, breathlessness and wheeze occurring from time to time. With progression of the disease, the intervals between the exacerbations become shorter, and in the later stages, hypoxaemia and cyanosis result. Viral and bacterial infections and air pollution cause exacerbations of COPD and indicate worsening of the underlying chronic inflammation of the airways [16], and the frequency of the exacerbations is one of the important determinants of health-related quality of life [17]. The rate of decline is also influenced by several factors such as age, smoking status, airway hyperresponsiveness, resting heart rate and hypoxaemia [6], pulmonary hypertension, cor pulmonale and death (Fig 1).

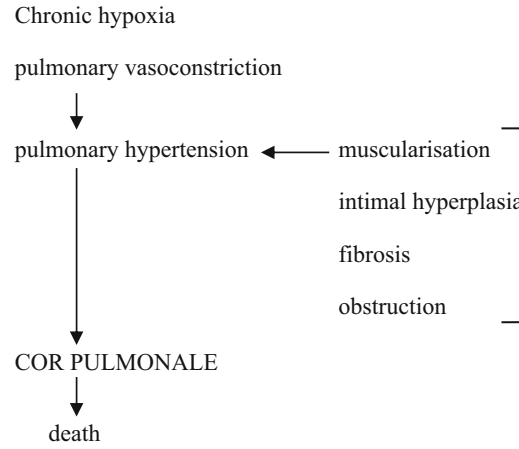

Fig. 1 Vascular changes in COPD

Management of Stable COPD

Cessation of Smoking

It has been shown that the smoker who quits before the age of 50 years may be able to reverse the risks, and furthermore those who quit after the age of 60 may reduce the risk of dying by 39% [18]. Cessation of smoking is one of the most important aspects of management of COPD and confers many benefits. Available strategies for cessation of smoking include (i) nicotine replacement therapy (which is available as patch, gum, lozenges and inhaler) and bupropion (an antidepressant), (ii) smoking cessation programmes, (iii) counselling, (iv) behavioural intervention or (v) a combination of these.

It is necessary to realise that cigarette dependence is a chronic relapsing condition and often involves a long or even a lifetime struggle to achieve success. To begin with it would be necessary to know whether the individual has a real desire to stop. Next it would be necessary to assess the degree of dependence which is based not only on the number of cigarettes per day but also the pattern of smoking during the day. Smoking in the first hours of waking suggests a greater degree of dependence.

Nicotine Replacement Therapy (NRT)

Completely ceasing to smoke remains the ideal goal. The Guidelines for Healthcare Professionals on using nicotine replacement therapy for smokers not yet ready to stop smoking recommends a new indication for two nicotine replacement therapy products, gum and inhaler. This allows smokers to cut down on their smoking with a view to stopping later [19]. An individual who smokes more than 20 cigarettes per day and has to have his first cigarette within 30 min of waking up is very likely to require nicotine replacement therapy or bupropion. Nicotine is the addictive element in the cigarette. Withdrawal from nicotine may cause unpleasant symptoms

such as depression, insomnia, dysphoria, restlessness, irritability, anxiety, difficulty in concentration, appetite increases and weight gain (Box 3). General measures [20] over several months and their effects are more likely to occur within the first week of cessation. Most residual symptoms improve within a month, but hunger and weight gain may persist for longer. Nicotine replacement therapy is used to ameliorate nicotine withdrawal. The nicotine patch or gum provides about 40% of the nicotine found in cigarettes but are not accompanied by the carcinogens and carbon monoxide.

Nicotine replacement is instituted after proper medical assessment. Contraindications are hypersensitivity, recent cerebrovascular accident, recent acute myocardial infarction and severe cardiac arrhythmias. There is now considerable evidence that NRT use in smokers with cardiovascular disease does not pose a risk [19]. The guidelines recommend that in view of the potential to trigger cardiovascular events, persons who are under active management by a cardiologist or cardiac surgeon, the clinician should be involved in prescribing or dispensing NRT [20].

Nicotine patches are applied to the skin; nicotine gum and lozenges allow nicotine to be slowly released in the mouth and nicotine inhaler delivers a puff. Nicotine patches have a recommended schedule in healthy patients: 21 mg /day for 6 weeks, 14 mg /day for the next 2 weeks and 7 mg/day for the final 2 weeks, and duration of treatment should not exceed 3 months. The patch should be applied on non-hairy, clean, dry skin in the upper body. Most patients require nicotine gum 16–24 mg daily and nicotine inhaler 6–12 cartridges/day (10 mg per cartridge).

Bupropion (Zyban) is an antidepressant. Treatment is usually started when the patient is still smoking, and the target stop date is set within the first 2 weeks of treatment with Zyban preferably in the second week, and duration of treatment is approximately 7 weeks. Contraindications are hypersensitivity, cerebral tumour, history of head trauma, seizure, alcohol misuse, patients with anorexia nervosa or bulimia, bipolar disorder and diabetics on hypoglycaemic agents or insulin [21]. Combination therapy: Randomised control trials have shown that combination therapy (nicotine replacement + bupropion) had a greater likelihood of achieving smoke-free states than either alone [22] (Table 1):

(i) Smoker cessation programme. There must be a commitment to stop with an aim of total abstinence. A date should be fixed for quitting. The pattern of smoking should be identified and triggers identified. Nicotine replacement therapy should be initiated, and there should be open communication to minimise non-compliance or failures. Helpful strategies include avoiding stress, stopping anybody else from smoking in the house and avoiding places or situations where they automatically smoke.

Table 1 Nicotine replacement therapy

Type	Dosage strengths	Daily dose	Administration	Adverse reactions
Transdermal patch	7, 14 and 21 mg	Used every 16 or 24 h[a]	To skin	Skin reactions or rashes
Nicotine gum/lozenge	2 or 4 mg	10 times/day	Chewed between, cheek and gum	Mouth soreness dyspepsia
Nicotine inhaler	~4 mg	10 or more	Through mouth piece	
Bupropion	150 mg	150 mg daily for 3 days thereafter bd	Orally	Nausea, vomiting, dry, mouth, insomnia

Each cigarette may contain up to 14 mg of nicotine, but smokers extract 1 mg of nicotine per cigarette independent of the brand

[a]Initial strength of dosage will depend on severity of dependence as well as on the number of cigarettes/day

(ii) Counselling. Counselling with aggressive smoking intervention with nicotine patches in the Lung Health Study participants allowed 22% of them to achieve sustained cessation over 5 years, and 93% of the individuals were still abstained at11 years [7, 23].
(iii) Behavioural therapy.

As an adjunct to smoking cessation programmes, behavioural intervention as individuals or as a group and behavioural techniques as hypnosis may be useful.

Pharmacological Interventions

Bronchodilators

There may be a degree of reversibility in some patients with COPD. Unlike that in asthma, the bronchoconstriction is mainly located in the small airways and is not due to increase smooth muscle activity as in asthma. The bronchoconstriction that results from inflammation may also produce some degree of reversibility. Patients with symptoms of COPD but reversibility as in the asthma should be managed as for diagnosis of asthma. Bronchodilators used in COPD treatment [24] include beta-adrenergic agonists, anticholinergics [25, 26] and methylxanthines [15].

Inhaled bronchodilators including beta-2 agonists and muscarinic receptor antagonists are the mainstay of treatment of stable COPD [27, 28], and this combination has been shown to be more effective because of their different modes of action [26]. Long-acting bronchodilators are more effective for maintenance of patients with moderate and very severe COPD [26]. More recently long-acting beta-2 agents (LABAs) and muscarinic antagonists (LAMAs) are recommended for regular use either alone or concurrent therapy in COPD [24, 25]. A combination of formoterol with long-acting antimuscarinic tiotropium bromide once or twice daily improves airway obstruction [24]. Unlike in asthma in COPD, inhaled corticosteroids should be considered in the later stages of the disease. In moderate to severe COPD, inhaled corticosteroids have an anti-inflammatory effect and reduced exacerbations [29]. Although there is a place for high-dose inhaled corticosteroids in COPD, using them continuously can cause adverse effects. They should be reviewed and discontinued 4–8 weeks after commencement if there is no response [29]. The use of inhaled corticosteroid (ICS) therapy has been established in the treatment of COPD, and ICS acts on the inflammation but is less effective in severe COPD [30]. Superior control has been shown with inhaled corticosteroids (ICS) and LABA therapy [31, 32], and the combination products are budesonide/formoterol (Symbicort) and salmeterol/fluticasone propionate (Seretide) [27, 33]. This combination has been shown to be effective, safe and convenient [33]. Local side effects of ICS include hoarseness and oral candidiasis, and systemic side effects include easy bruising and are due to use of above maximum recommended doses [30]. The treatment goals are summarised in Table 2.

Non-pharmacological Interventions

Oxygen Therapy

Pulse oximetry can be used to monitor oxygen saturation, and oxygen saturation is maintained at 90% or higher. Oxygen is delivered by nasal cannula or face mask. With severe exacerbations intubation or continuous positive airway pressure (CPAP) may be necessary to sustain adequate oxygenation.

Long-Term Oxygen Therapy

Long-term oxygen therapy will improve survival, reduce frequency of hospitalisation and improve exercise tolerance and quality of life (Box 1). The patient should be referred to a respiratory physician. Supplementary oxygen should be given to patients who are hypoxaemic with PaO_2 of 55 mmHg or less or an oxygen saturation of 88% or less while sleeping. It should be considered in patients (Box 2). Oxygen therapy at home can be delivered by nasal cannula or CPAP; the latter is generally reserved for patients with chronic hypercapnia.

Table 2 Treatment goals and management

Goals	Management
I. Risk factor modification	Emphasis on cessation of smoking
	Counselling
II Amelioration of signs and symptoms	
i. Pharmacological interventions	Bronchodilator therapy, corticosteroids
	Minimise side effects of therapy
ii. Non-pharmacological interventions physiotherapy for bronchial hygiene, disease	Supplementary oxygen, exercise, nutrition education
III. Management of complications	Treatment of heart failure
	Treatment of respiratory failure possibly by mechanical ventilation
IV. Prevent and treat exacerbations	Antibiotics, immunisation, referral to hospital
V. Optimise patients longevity, improve functional status and quality of life	Pulmonary rehabilitation
	Long-term oxygen therapy
	Possibly palliative surgery (lung volume reduction surgery), lung transplant

Information Sources: Barnes [9], Sutherland and Chermiak [34]

Box 1 Benefits of Long-Term Oxygen Therapy

- Improves survival
- Improves quality of life
- Reduces frequency of hospitalisation

Source of information: Nocturnal O_2 Therapy Trial Group (1980)

Box 2 Indications for Long-Term Oxygen Therapy

Marked hypoxaemia [PaO_2 <55 mmHg or SaO_2 <88%]

Box 2 Indications for Long-Term Oxygen Therapy (continued)

Severe recurring secondary erythrocytosis [haematocrit >55%]

Pulmonary hypertension

Right-sided heart failure

Severe exercise dyspnoea and fatigue and correlating with lowered arterial O_2 tension

Impaired cognitive processes which improve with O_2 therapy

Insomnia and/or listlessness corrected by O_2 therapy

Pulmonary Rehabilitation

Pulmonary rehabilitation embraces the following: cessation of smoking; physical, nutritional and occupational therapy; patient and family education; and the selection of patients for long-term oxygen therapy [15]. Pulmonary rehabilitation may benefit patients with limited activity and decreased quality of life. It augments standard medical therapy and improves functional capacity and exercise tolerance and is used in patients whose response to pharmacological interventions is suboptimal.

Management of Acute Exacerbations

An acute exacerbation is characterised by an acute onset, sustained worsening from the baseline functional status and more than the usual day-to-day variations, requiring additional treatment [16, 35]. The exacerbation is most likely to be due to viral or bacterial infections, and *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* continue to be the predominant organisms. Depending on the severity of the stable state, acute exacerbation may present with increased cough, increase in purulent sputum and breathlessness with or without fever [15]. The most notable determinant is whether the patient

requires hospitalisation or can be treated as an outpatient. Patients who have significant clinical evidence of respiratory distress or one who has a previous history of severe exacerbations will require hospital admission. The strategies for management of acute exacerbations are similar to that used in the stable COPD. They include oxygen, bronchodilators, antibiotics, systemic corticosteroids [15] and mechanical ventilators [6].

Impact

Chronic obstructive airways disease (COPD) is a chronic progressive disease and is common in older people. The prevalence and mortality of COPD increases with age [36]. It is the fourth major cause of mortality in the developed world [37]. It causes a number of problems in everyday life such as progressive dyspnoea, fatigue, cough, exercise intolerance, recurrent exacerbations [36], disturbed sleep and poor appetite, all of which have a negative impact on the quality of life (QoL) [38–40]. There is a significant impairment of QoL in the elderly with COPD depending on the severity of airway obstruction [41]. The EPIDEPOC study has shown a negative impact of COPD on HR-QoL [37]. The severity grade (GOLD criteria) and the duration of hospital stay correlated significantly with overall costs. According to the study, costs were mostly due to hospital admissions resulting from acute exacerbations and to outpatient drug use [42]. In America and Europe, COPD subjects older than 65 years tend to underestimate their illness as shown by a large proportion of them having limitation of activities of daily living and frequent use of health resources [43]. Patients with moderate and severe COPD experience acute exacerbations, and patients' QoL is related to the frequency of these exacerbations [44]. Acute exacerbations accelerate the disease progress and mortality [45]. It is the major cause of morbidity and mortality with 50% mortality at 3.6 years and 75% at 7.7 years and 96% at 17 years [46].

Co-morbidity is an important consideration in patients with COPD particularly in older patients, and timely treatment could lessen the important effects on the health status [47]. Patients with COPD and impaired cognition have a higher rate of hospitalisation for all causes and higher risk of death [48]. COPD patients experience psychological distress and impaired cognitive function [49, 50], with increased disability and morbidity and impaired QoL. The prevalence of co-morbidity associated with cardiovascular disease and cancer is significantly high in the elderly with COPD [51] and has drawn much attention. In early stages of COPD, there may be an impact on left ventricular function and severe COPD effects on right ventricular function [52]. The coexistence of COPD and heart failure increases with age, and COPD however did not alter survival [53]. QoL and work productivity are severely affected among employed adults aged 65 years and older with COPD [54].

Box 3 Key Points. COPD

Ageing of the population and past smoking are the major causes of the increase in COPD [1].

Spirometry is the most useful measure of outflow obstruction [9] and indispensable in establishing the diagnosis because it is a standardised and reproducible test that objectively confirms the presence of airflow obstruction.

The FVC and FEV_1 are both decreased, but FEV_1 is reduced to a greater degree causing a reduction in the FEV_1/FVC ratio [13, 14].

Cessation of smoking is one of the most important aspects of management of COPD and confers many benefits.

Bronchodilators used in COPD treatment [24] include beta-adrenergic agonists, anticholinergics [25, 26] and methylxanthines [15].

(*continued*)

Box 3 Key Points. COPD (continued)

An acute exacerbation is characterised by an acute onset, sustained worsening from the baseline functional status and more than the usual day-to-day variations and requires additional treatment [16, 35].

The strategies for management of acute exacerbations are similar to that used in the stable COPD.

Pulmonary rehabilitation embraces the following: cessation of smoking; physical, nutritional and occupational therapy; patient and family education; and the selection of patients for long-term oxygen therapy [15].

Multiple Choice Questions

1. The following in COPD are true *except*:
   A. Ninety percent of COPD are caused by cigarette smoking, and less than 50% of smokers develop significant airway obstruction.
   B. In cigarette smoke susceptible to COPD, the rate of decline as measured by FEV_1 is three- to fivefold than compared to age-related rate.
   C. Smokers with a family history of airway obstructive disease are more likely to develop COPD.
   D. Airways limitation is generally progressive and the rate of decline is variable.
2. In COPD the following findings are true *except*:
   A. In COPD there is prolonged expiration with generalised wheezing predominantly on inspiration.
   B. In blue bloater type of COPD, the PO_2 is less than 65 mmHg.
   C. In the pink puffer type of COPD, the PCO_2 is usually normal.
   D. Ultimately COPD is complicated by hypoxaemia, intimal thickening and pulmonary hypertension.
3. In COPD the following are true *except*:
   A. Spirometry is indispensable in establishing the diagnosis.
   B. FVC and FEV_1 are both decreased, but FEV_1/FVC ratio is normal.
   C. FEV_1 <35% predicts COPD is severe.
   D. Measuring the diffusion capacity for carbon monoxide (DLCO) is helpful in the context of fixed airflow obstruction; a decrease indicates loss of alveolar-capillary areas suggesting emphysema.
4. The following are true in COPD *except*:
   A. *Staphylococcus aureus* infection during the influenza season can cause acute exacerbation.
   B. Pharmacological interventions in COPD include brochodilators and corticosteroids.
   C. Hypoxaemia $PO_2 < 55$ mmHg/$SaO_2 < 88\%$ is an indication for long-term oxygen therapy.
   D. Post-bronchodilator spirometry is not required to confirm a diagnosis of COPD.

MCQ Answers

1 = A; 2 = A; 3 = B; 4 = D

Case Study of a Patient with Acute Exacerbation of COPD

Presentation: A 72-year-old man presented to hospital with increasing shortness of breath, cough, slight wheeze, increasing quantity of yellow sputum and fever over 5–6 days preceded by sore throat and runny nose. Symptoms had worsened over the past 2 days. He has been smoking for more than 50 years and continues to smoke. He gave no history of chest pain, calf pain or swelling of the legs. Past history includes a chronic cough and increasing breathlessness over the past 7–8 years. He was on a bronchodilator. He was tachypnoeic using his accessory muscles. Air entry was decreased bilaterally, with wheezes and basal crackles (pO_2 60, mmHg; pCO, 54 mmHg; O_2 saturation, 78%; FEV_1/FVC, 0.80/1.80 litres; white cell count: neutrophils, 88%; chest X-ray, hyperinflated lung fields and no other abnormality; sputum culture, *H. influenzae*).

Comment: His current symptoms were a departure from his usual day-to-day variation. He has

had similar episodes in the past and had to be hospitalised on a few occasions, and these events seem to occur with increasing frequency. Acute exacerbation of COPD is defined as an incident distinguished by a difference in the symptoms and signs from the usual day-to-day variation and not due to such conditions as pulmonary emboli, pneumothorax, pneumonia or congestive heart failure. They are caused mainly by bacterial or viral infections or air pollution. The presence and frequency of acute exacerbations signal respiratory decompensation and the state of health of patients with COPD. The most notable determinant is whether the patient requires hospitalisation or can be treated as outpatient. The treatment includes oxygen, bronchodilators, antibiotics, systemic corticosteroids and mechanical ventilators [6, 15].

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Asthma in the Elderly

10

Contents

Abstract

In the elderly, asthma is superimposed on changes related to ageing, immune function and other diseases common in older age. The aetiology of asthma in the elderly is multifactorial and complex. One-third of the older patients experience breathlessness which is a non-specific symptom in the elderly, and the differential diagnosis includes, besides asthma, COPD and non-respiratory conditions such as cardiac failure, deconditioning, obesity and infection, amongst others. Cough is a prominent symptom in the elderly asthmatics and may be the only symptom. The difficulty of making a diagnosis in the elderly is due to a number of factors. Spirometry has been used as a 'gold standard' in the diagnosis of asthma but there a number of limitations especially in the older patient. Asthma is common in the elderly and often is misdiagnosed, underdiagnosed and undertreated resulting in significant negative consequences for the patient's health.

Keywords

Elderly asthma · Late-onset asthma · Spirometry · Beta-agonists · Antimuscarinics

Introduction

There is an increased mortality and morbidity amongst a significant number of older asthmatics due to poorly controlled asthma [1]. In the elderly, asthma is superimposed on changes related to ageing, immune function and other diseases common in older age [2]. In elderly patients with

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_11

asthma, there are at least two phenotypes, those with long-standing asthma and those with late-onset asthma [2]. The former has more severe airflow limitation and recovery is less complete [2]. The aetiology of asthma is multifactorial and complex. Asthma in the elderly is often associated with allergic triggers. Late-onset asthma in older adults has been identified with household dust mites [3] and sensitisation to cat allergen [4]. Elderly asthmatic patients have been found to have been sensitised to cockroach antigen, and these patients may have an increased risk for asthma morbidity [5]. Respiratory tract infections are major precipitating factor in elderly asthmatics [6].

Symptomatology

One-third of the older patients experience breathlessness which is a non-specific symptom in the elderly, and the differential diagnosis includes, besides asthma, COPD and non-respiratory conditions such as cardiac failure, deconditioning, obesity and infection, amongst others [7]. Cough is a prominent symptom in the elderly asthmatics and may be the only symptom [8, 9] but may also be due to reflux or postnasal drip. Making the distinction between asthma and COPD is important for management. Furthermore, with long-standing asthma, the disease may be difficult to distinguish from COPD [10]. Childhood infections, obesity, smoke and allergy influence adult-onset asthma, whereas the risk factors for COPD are adult tobacco and biomass smoke [11]. Patients with symptoms of COPD but reversibility in the asthma range should be managed as for a diagnosis of asthma.

There have been suggestions to differentiate asthma on the basis of age at onset, early vs late [12]. Studies have been inconsistent and debatable. Early-onset severe asthma is associated with more allergen sensitivity and more allergic symptoms and with a lymphocytic/mast cell inflammatory process [12]. The late onset has lower lung function and increased number of lung eosinophils, and those without eosinophils had no thickening of the subepithelial basement membrane [12]. The late-onset group has worse prognosis and poor response to standard asthma treatment [13].

Diagnosis

The difficulty of making a diagnosis in the elderly is due to a number of factors, and these include (i) poor perception of the signs and symptoms, perceived as part of normal ageing [8]; (ii) technical difficulties in making reliable pulmonary function measurements [14]; (iii) presence of extra-pulmonary manifestations; (iv) effects of ageing on the airways – changes to innate immunity [15]; (v) co-morbidity may mask the classical symptoms of asthma; and (vi) patients underrating their symptoms. In one cardiac centre, up to 20% of patients with cardiomyopathy were treated with beta-agonists before the correct diagnosis was made [16]. In one study, 19.5% of patients (mean age of 73 years) were wrongly diagnosed as COPD [17]. COPD is the condition that causes diagnostic difficulties in older patients with asthma [8].

Spirometry has been used as a ‘gold standard’ in the diagnosis of asthma, but there a number of limitations especially in the older patient. (i) This test is operator dependent, and there is a need for better understanding how to achieve accurate office-based spirometry in elderly people [18]. (ii) Peak expiratory flow rate is more difficult in older people [19] which may be limited by age-related factors such as perceptual and motor skills required for accurate measurement. (iii) Because of the decreased number of beta-adrenergic receptors in the bronchial smooth muscle in old subjects [20], there may be a blunted bronchodilator response which may reflect the pathophysiology of COPD rather than that of asthma. Post-bronchodilator spirometry is required to confirm a diagnosis of asthma. Fifteen percent of the older people are not able to undergo spirometric tests or peak flow expiratory flow rate [21], and spirometry reference rates for older people only apply to 85 years or under [22]. Elderly people tend to underrate their symptoms, and this is confounded by other medical illnesses and access to care. Less than 25% of elderly patients presenting with cough and breathlessness will be tested [23].

Management

Beta-Agonists

There are several types of beta-2-agonists, most are pharmacologically similar. Salbutamol (Ventolin) and terbutaline sulphate (Bricanyl) are the two commonly used bronchodilators. Other less common drugs used are fenoterol (Berotec), formoterol (Foradil) and salmeterol (Serevent). Salbutamol is a relatively selectively beta-adrenergic stimulant. After oral and parenteral administration, both beta-1 and beta-2 beta-receptors are stimulated, and higher concentrations of salbutamol occur in the regions of these receptors. The beta-1 effects of cardiac stimulation and beta-2 effects of peripheral vasodilatation, skeletal muscle tremor and uterine muscle relaxation occur with these modes of administration.

All beta-2-agonists are administered by inhalation of the drug as an aerosol (either from a nebuliser or a metered dose inhaler) or as a powder delivery system such as the Turbuhaler and Rotacaps. After inhalation salbutamol acts topically on the bronchial smooth muscle and initially the drug is undetectable in the blood. After 2–3 h, the concentration is seen to be of the stage as if swallowed and absorbed by the gut. By using a large volume spacer (Volumatic or Nebuhaler), the percentage distribution can be improved. The maximum therapeutic effect is seen in 15 min of inhalation. Terbutaline is a selective stimulant of the pulmonary $beta_2$-receptors and relatively a minor stimulant of cardiac beta-1-receptor. Its effect is rapid in onset and reaches a maximum in 30 min after subcutaneous injection, 1 h after inhalation and 2–3 h after oral administration. The duration of an action is between 4 and 5 h. It is also known to improve mucous clearance.

Long-acting $beta_2$-agonists (LABA) such as salmeterol and formoterol have different chemical structures with different mechanisms of action [24]. Salmeterol belongs to a new class of selective long-acting beta-2-adrenergic receptor agonists. At doses less than 100 mcg/bd, it has little cardiovascular effects. Formoterol (Foradil) is a new class of potent long-acting selective $beta_2$-adrenergic receptor agonist with onset of rapid action [24]. The onset of bronchodilatation occurs within 1–3 min and is still significant 12 h after inhalation. The time peak effect is 1–2 h. Its cardiovascular effects are minor. LABA can be used earlier in the therapy as an alternative to other bronchodilators.

Antimuscarinics

Antimuscarinics act as muscarine acetylcholine receptor antagonists [25]. Ipratropium bromide (Atrovent) a prototype of antimuscarinic bronchodilators is short acting which [25] differs fundamentally from the $beta_2$-agonists in that it allows bronchodilatation by inhibiting cholinergic bronchomotor tone; vagal reflexes which mediate bronchoconstriction are blocked. The bronchodilatation effect with ipratropium is primarily a local site-specific effect. The time course also differs from the $beta_2$-agonists in that it allows the onset of bronchodilatation within 3–5 min of administration, and the peak is not reached till 1.5–2 h after inhalation. The duration of significant bronchodilatation is up to 16 h. It may be used with beta-2-agonists, and the concurrent use produces a greater relief of bronchospasm than when either drug is given alone. Tiotropium bromide is a long-acting antimuscarinic agent (LAMA) and is administered once a day [25].

Reliance on the use of long-term preventive therapy with inhaled corticosteroids in place of shorter-acting bronchodilator drugs is the trend in recent years in the management of persistent asthma in the elderly. The inhaled shorter-acting beta-agonists can be used as rescue medication [1]. Inhaled corticosteroids (ICS) are recommended as the first-line therapy in symptomatic asthma, and in the case of poor asthma control, long-acting beta-agonist (LABA) can be added. LABA should not be used alone as a monotherapy because of the association between LABA monotherapy and asthma-related hospital admissions and deaths [26–28]. LABA when combined with inhaled corticosteroids improve asthma symptoms and lung functions and reduce exacerbations [29]. When symptoms are more severe, oral corticosteroids should be given.

Patients vary in their response to inhaled corticosteroids (such as budesonide, beclomethasone, fluocinonide, fluticasone and mometasone), and adverse effects follow a clear dose-response relationship. The correct dose for inhaled corticosteroids should be ascertained by regular monitoring and titration, and when asthma control is attained, the dose should be back titrated to the lowest effective dose [27]. Consistent use of inhaled corticosteroids can improve asthma symptoms, frequency and severity of exacerbations and quality of life [30]. Recently, in patients with frequent symptoms despite being on conventional combination therapy or corticosteroid alone, an alternative regimen has been recommended. Budesonide/formoterol dry powder inhaler (Symbicort Turbuhaler) and salmeterol/fluticasone propionate (SeretideTM) had been introduced [31] and can be used for both maintenance dosing and on demand in response to acute asthma symptoms [27]. An ICS/LABA combination in a single inhaler is safe and effective treatment for patients with asthma [31].

During the last decade, our knowledge and understanding of the biological pathways and identification of specific phenotypes have led to recognition of potential targets for innovative therapeutic avenues in asthma. Biologic agents aimed at modulating cell signalling and the immunologic responses have provided evidence of capability of changing the management of asthma [32]. Several new classes of asthma drugs including modulators of interleukin 4 (IL-4), IL-5, Il-13 and IL-17 pathways have been evaluated in clinical trials [32]. Omalizumab, a humanised antibody directed against IgE is an option for severe allergic asthma [13]. Mepolizumab and reslizumab monoclonal antibodies target IL-5 pathway inhibiting eosinophilic airway inflammation [13, 32].

Impact

Asthma is common in the elderly and often is misdiagnosed, underdiagnosed [33, 34] and undertreated [35] resulting in significant negative consequences for the patient's health [36]. In the elderly, the asthma is more severe and is associated with faster decline in lung function [37] with increased dyspnoea and reduced ability for activities of daily living. Psychosocial burden is often unrecognised, and there is a high risk of anxiety and depression and lower self-reported quality of life [8]. In the elderly, the burden of co-morbidities and increased hospitalisation [2, 33] results in increased burden on patients and medical costs [27]. Greater proportion of hospital admissions (23%) are in the 65 years and older age group compared to the size of its population (13%) [2]. There is a significant impact on the quality of life with 35% with definite or potential asthma reporting a fair or poor health status compared to 17% of the elderly without asthma [2]. Compared with younger asthmatics, older asthmatics are associated with co-morbidities, in many a fixed airflow obstruction and lack of perception often causing a delay in diagnosis [38]. There is a higher risk of allergic sensitisation, decreased lung function and significant worse quality of life in older asthmatics [39] (Box 1).

Box 1 Key Points: Asthma in the Elderly

In at least half of the elderly patients, the asthma is recently acquired.

Asthma in the elderly is often associated with allergic triggers.

Late-onset asthma in older adults has been identified with household dust mites [3] and sensitisation to cat allergen [4].

Respiratory tract infections are major precipitating factors in elderly [6].

In the elderly, long-standing asthma may be difficult to distinguish from COPD [27].

Spirometry has been used as a 'gold standard' in diagnosis of asthma [18].

Fifteen percent of the older people are not able to undergo spirometric tests or peak flow expiratory flow rate [21], and spirometry reference rates for older people only apply to 85 years or under [22].

(*continued*)

Box 1 Key Points: Asthma in the Elderly (continued)

LABA when combined with inhaled corticosteroids improve asthma symptoms and lung functions and reduce exacerbations [29].

Multiple Choice Questions

1. The following are true of asthma in the elderly, except:
   A. In at least half of the elderly patients, asthma is recently acquired.
   B. In one study, 20% of the elderly patients with asthma were wrongly diagnosed as COPD.
   C. Asthma in the elderly is often associated with allergic triggers.
   D. Asthma in the elderly results from effects of ageing on the airways.
2. The following are true of asthma in the elderly, except:
   A. Elderly people tend to underrate their symptoms, and this is confounded by other medical illnesses and access to care.
   B. Spirometry reference rates for older people only apply to 85 years or under.
   C. More than half of the elderly are not able to undergo spirometric tests or peak flow expiratory flow rate.
   D. Because of the decreased number of beta-adrenergic receptors in the bronchial smooth muscle in old subjects, there may be a blunted response to bronchodilator spirometry.
3. The following are true in the management of asthma in the elderly, except:
   A. Inhaled corticosteroids are recommended as the first line-therapy in symptomatic asthma.
   B. If there is poor asthma control, long-acting beta-agonist (LABA) can be used concurrently.
   C. LABA can be used alone as a monotherapy.
   D. Budesonide with formoterol dry powder inhaler (Symbicort Turbuhaler) can be used for maintenance dosing and on demand in response to acute asthma symptoms.

MCQ Answers

1 = D; 2 = C; 3 = C

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Lung Cancer in the Elderly

11

Contents

Abstract

Lung cancer is characterised as cancerous growth in the lungs which may be primary, originating from the lung cells, or secondary, metastatic from another source. In the United Kingdom, the peak incidence of lung cancer is between 75 and 80 years of age. Between 30% and 45% of all lung cancers are diagnosed in patients older than 70 years. Many of the symptoms in the elderly are non-specific such as fever and loss of weight and often attributed to co-morbid illnesses. Paraneoplastic phenomena associated with certain types of tumour may be the first indication of lung cancer. In evaluating mediastinum, magnetic resonance imaging (MRI) of the chest is somewhat equal to that of CT but is generally superior in determining chest wall or vertebral body involvement. The treatment of lung cancer will very much depend on the cell type, the extent of spread and the patients' performance status. Commonly, treatment includes surgery, chemotherapy and radiotherapy. Treatment outcomes in the elderly are largely influenced by the presence of co-morbid conditions, and the elderly have the highest rates of co-morbidities, age-related decline in organ function and the ability to tolerate treatment.

Keywords

Lung cancer · Mutation of KRAS proto-oncogenes · Paraneoplastic phenomena · Non-small cell lung carcinoma (NSCLC) · Small cell lung carcinoma (SCLC) · TNM staging system

Introduction

In the United States, lung cancer remains the leading cause of cancer death in both men and women. The incidence of lung cancer in the United States will continue to rise because of the long latency between initiation of smoking and occurrence of the disease [1]. It is the most

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_9

common cause of cancer-related death in men and the second most common cause in women [2] and is responsible for 1.3 million deaths worldwide annually [3]. It is the leading cause of death in many Western countries [4]. Lung cancer mortality has increased in those 65 years and older during the period 1980–1998, has decreased in younger than 55 years reflecting generational patterns in smoking prevalence [5] and is not uncommon in persons older than 85 years [6]. Lung cancer mortality rates in men will continue a downward trend during the first part of the century as the result of the reduction in smoking prevalence in men that are born in the late 1960s to the 1980s [7].

The known behavioural and environmental causes include cigarette smoking, asbestos, other occupational carcinogens, radon, environmental tobacco smoke, air pollution and pre-existing non-malignant disease [8]. Genetic factors may play a modifying risk in individual's risk for lung cancer [9]. Lung cancer incidence largely mirrors smoking prevalence [8]. The incidence is likely to increase in India [10] and in China [11] due to increased smoking. About 90% of the lung cancer deaths is caused by smoking across the developed world [12]. Patients who smoke at the time of diagnosis have a shorter survival than those who have ceased smoking [13].

Symptomatology

Symptoms and signs of lung cancer will depend on (i) the location of the tumour, (ii) the manner of spread and (iii) the type of tumour. Lung cancers are largely endobronchial and a common presentation is cough with or without haemoptysis. Peripheral nodular tumours are asymptomatic till they invade the pleura and chest causing pain. About 7–10% of lung cancers are asymptomatic and diagnosed incidentally after a chest X-ray was done for other reasons [14]. Many of the symptoms in the elderly are non-specific such as fever and loss of weight and more often attributed to co-morbid illnesses [15].

Pancoast tumours situated at the apex may give rise to Horner's syndrome as well as weakness and pain in the arm on the affected side due to involvement of the sympathetic nerve and the brachial plexus. The tumour may extend directly to obstruct the oesophagus causing dysphagia, extend to involve the superior vena cava giving rise the superior vena cava syndrome [16], and involve the heart causing pericardial effusion, cardiac tamponade and arrhythmias. Involvement of the left recurrent laryngeal nerve causes hoarseness, and involvement of the phrenic nerve causes paralysis of the diaphragm.

Paraneoplastic phenomena associated with certain types of tumour may be the first indication of lung cancer. They occur in up to 10% of patients with lung cancer. Small cell lung cancer (SCLC) is associated with paraneoplastic manifestations. Common paraneoplastic syndromes associated with lung cancer are syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [17], hypercalcaemia, Cushing's syndrome and neurologic syndromes such Lambert-Eaton myasthenic syndrome (LEM) (Box 1). Sixty-seven percent of SIADH is associated with cancer of which 70% are linked with SCLC [17]. LEM is linked with SCLC in 60% of cases [18] and other paraneoplastic neurologic syndromes (PNS) in 5% of SCLC [19]. Hypertrophic osteoarthropathy (HOA) particularly clubbing is seen in about 10% of lung tumours [20]. Lung cancer can metastasise virtually to any bone, liver, adrenal glands, intra-abdominal lymph nodes, brain and spinal cord. Bone pain is present in about 25% of all patients at presentation [21]. Table 1 shows the lung cancer characteristics based on histologic classification.

Box 1 Paraneoplastic Phenomena
Hypercalcaemia
Hypophosphataemia
SIADH
Cushing's syndrome
Eaton-Lambert myasthenic syndrome
Peripheral neuropathy
Spino-cerebellar degeneration
Polymyositis
Disseminated intravascular coagulation
Migratory thrombophlebitis

Table 1 Lung cancer characteristics based on histologic classification

Histological type	Incidence approx.	Gender ratio	Location and size	Other features	Rate of growth and spread	Histology	Prognosis
I. Non-small cell lung cancer	80–85%						
(i) Squamous cell carcinoma	25–30%	Men > women	Central large	Cavitation necrosis, strong association with smoking	Slow, late metastasis	Well-to-poor differentiation squamous-cell keratin pearls	Generally poor
(ii) Adenocarcinoma	30–35%	Men > women	Peripheral small masses	Weak association with smoking	Slow, early metastasis and widely	Cuboidal to columnar cells secrete mucin	Different response to treatment
(iii) Large cell carcinoma	10–15%		More peripheral than central		Fast, spread to distal sites	Poorly differentiated anaplastic	Poor, 5-year survival rate 2–3%
II. Small cell carcinoma	15–20%	Men > women	Central small	Paraneoplastic phenomena, strong association with smoking	Rapid, early dissemination	Small, round dark cells	Poor, 2-year survival rate 5–8%

Information sources: Barbone et al. [22] and Veronesi et al. [23]

Diagnosis

Evaluation of a patient for lung cancer includes a medical history of smoking, history exposure to environmental and occupational substances and a family history. This is followed by an X-ray of the chest and CT scan. Two frequent clinical presentations are pneumonia and an abnormality on the chest X-ray and no symptoms. About 25% of the patients are asymptomatic at the time of presentation. Simple pneumonia undergoes complete resolution within a few weeks. Pneumonia in a patient in the cancer age which remains unchanged for more than 2–3 weeks or improves partially on appropriate antibiotic therapy or a pneumonia recurring on the same lobe may be indicative of an underlying carcinoma.

The chest X-ray may not reveal any lesion but more often shows a mass, consolidation, atelectasis, hilar mass or pleural effusion and plays a pivotal role in the recognition of lung cancer. The differential diagnosis includes infections such as pneumonia, tuberculosis or inflammatory conditions such as sarcoidosis and may present as pulmonary nodule or mediastinal lymphadenopathy [15]. Lesions greater than 3 cm are usually considered as masses. Lung nodules can be benign or malignant and can have a number of causes [24–26] (Box 2).

Box 2 Factors Pointing Towards Malignancy and Solitary Pulmonary Nodule

I. Age: <35 years rare
   45 years considered malignant
   Till proved otherwise
II. Symptoms: cough, haemoptysis, clubbing, dyspnoea or neurological signs
III. Radiological
   (i) Size, shape, margin of lesion: lesions <2 cm with spherical shape and smooth margin more likely to be benign. Ill-defined margin suggestive of malignancy
   (ii) Pleural extension
      Calcification – "popcorn" (1/3 haematomas) and laminated specific for granulomas, central and parietal-benign, stippled or eccentric both
   (iii) Change in size-doubling time
      Squamous cell carcinoma ~100 days
      Adenocarcinoma ~180 days
      Bronchoalveolar carcinoma stable for long periods
IV. Organomegaly

Information sources: Lillington [24], Hanley and Rubins [25] and Winer-Muram [26]

The CT scan is more exact in determining hilar and mediastinal lymph node metastasis and also involvement of the adjacent structures manifesting as pleural effusion, pericardial effusion, mediastinal structures and invasion of the chest wall. However, about a third of the lung cancer patients may have false-positive findings as there is a high incidence of benign mediastinal lymphadenopathy in lung cancer patients. About one tenth may have false-negative findings. The CT scan for staging of lung cancer is extended into the abdomen to include the adrenal glands.

In evaluating the mediastinum, magnetic resonance imaging (MRI) of the chest is somewhat equal to that of CT but is generally superior in determining chest wall or vertebral body involvement. PET scan is also a useful adjunct for assessment. Other investigations include bronchoscopy and CT-guided fine needle biopsy. The American College of Chest Physicians (ACCP) guidelines for the initial diagnosis of lung cancer included the need to make a pretest probability of lung cancer based on CT appearance of the tumour and the need to make a tissue diagnosis of enlarged mediastinal lymph node if there is no evidence of disseminated disease [27]. A bronchoscopic method, the transbronchial needle aspiration (TBNA), is used to sample lymph nodes adjacent to the bronchus in the hilum and

mediastinum [28], and this has improved with the addition of endobronchial ultrasound (EBUS) [29].

Management

The treatment of lung cancer will very much depend on the cell type, the extent of spread and the patients' performance status. Commonly, treatment includes surgery, chemotherapy and radiotherapy. Staging is done to select treatment and to determine prognosis. Staging is described in terms of TNM system. According to this system, *T* is the tumour size; *N*, nodes involved; and *M*, metastasis status. The TNM staging system is not often used in the case of SCLC for the reason most of tumours would have suspect or definite metastasis at the time of diagnosis [30]. A major review of the TNM staging system has been made by the International Association for the Study of Lung Cancer (TASLC) [31]. The new classification is applicable to both types of lung cancers [32].

Treatment outcomes in the elderly are largely influenced by the presence of co-morbid conditions [33, 34], and the elderly have the highest rates of co-morbidities [35], age-related decline in organ function [33, 36] and the ability to tolerate treatment [36]. In the elderly, it is necessary to carry out a careful co-morbidity evaluation before deciding on the most acceptable therapeutic option [37]. In recent studies of patients' median age 70 years with lung cancer, 7.6% had COPD and 26.3% had combined cardiac and cerebrovascular disease [38, 39].

There is a bias based on age in that the elderly are not offered similar treatment to that of the younger patient [36]. There is considerable variation in the management of lung cancer and this is due to factors such as "ageism" [40]. In a review of the management of lung cancer in older adults, a number of issues were raised which were of particular relevance to elderly patients with lung cancer [41]. Questions that were raised and discussed were whether the patient with lung cancer died of the cancer or with the cancer, whether prognosis was affected by age and whether the usual treatment regimens will be tolerated by the elderly patients and in patients with incurable diseases the balance between survival and quality of life [6]. Resection rates decreased from 37% for patients below the age of 75 years to 15% for those older than 75 years in the United Kingdom [40].

If the primary NSCLC tumour is resectable, surgery is the treatment of choice. For tumours that are unresectable, the treatment is chemotherapy and radiotherapy. In elderly patients with advanced NSCLC, the usual accepted care is single-agent chemotherapy. In the case of SCLC which metastasises early and has a worse outcome than NSCLC, chemotherapy is the main treatment. More often than not, the diagnosis is made late into its natural history. Eighty patients out of 100 newly presenting patients with lung cancer will be inoperable at the time of presentation, and about 20 will proceed to attempt resection of whom five to ten will live for 5 years [42]. The 5-year survival rate can vary between 61% and 1% for patients with stage IA and IV disease, respectively, depending on the stage at diagnosis [43]. The rate of survival of patients is dependent on the histological subtype as well as the stage of the disease [44]. The median survival of advanced NSCLC ranges from 9 to 12 months [44].

Impact

The oldest old constitutes the fastest-growing segment of the population. About 47% of lung cancers occurred in 70 years or older and 24% in those above 80 years [205]. Because of the poor outcome, the very elderly are less likely to have surgery or radiation [45]. A significant proportion of the elderly patients 75 years or older are able to tolerate chemotherapy and have better survival [46]. However, many do not complete the treatment as outlined, and often treatment is modified or discontinued even for one or two low-grade toxicity [47]. Some studies indicate that there is increased risk of toxicity in older people [48], and increased toxicity is due to ageing [49]. Ageing is associated with increased co-morbidity [50], and it is believed that co-morbidity and not age is the major risk factor of toxicity [51]. According to Kalse et al. [47], this differentiation is important

for co-morbidity and is to an extent correctable. More recently, it has been shown that patients undergoing chemotherapy do exhibit cognitive impairment [52]. It has been reported that in the elderly with NSCLC and co-morbidity and poor prognosis, the efficacy of low dose and low toxicity with chemotherapy was justifiable [50] (Box 3).

Box 3 Key Points: Lung Cancer

About 7–10% of lung cancers are asymptomatic and diagnosed incidentally after a chest X-ray was done for other reasons [14].

Many of the symptoms in the elderly are non-specific such as fever and loss of weight and often attributed to co-morbid illnesses [15].

The differential diagnosis includes infections such as pneumonia, tuberculosis or inflammatory conditions such as sarcoidosis and may present as pulmonary nodule or mediastinal lymphadenopathy [15].

Treatment outcomes in the elderly are largely influenced by the presence of co-morbid conditions [33, 34], and the elderly have the highest rates of co-morbidities [35], age-related decline in organ function [33, 36] and the ability to tolerate treatment [36].

There is a bias, based on age, in that the elderly are not offered similar treatment to that of the younger patient [35].

Multiple Choice Questions

1. The following in relation to lung cancer are true, except:
   A. 65% of lung cancer occurs in persons in the 65 years and over.
   B. Mutations of K-ras proto-oncogenes are responsible for 20–30% of non-small cell lung cancer.
   C. Small cell lung cancer is associated with changes in several oncogenes and mutation of the raf gene.
   D. Small cell lung cancer is weakly associated with smoking.
2. The following are true with lung cancer, except:
   A. Smoking and other environmental factors are mainly responsible for the genetic changes which give rise to lung cancer.
   B. Squamous cell lung cancer has a strong association with smoking.
   C. Adenocarcinoma of the lung is located centrally and is large.
   D. Lung cancers are generally endobronchial.
3. The following clinical manifestations are true of lung cancer, except:
   A. Pancoast tumours are situated at the apex and give rise to Horner's syndrome and weakness of the arm.
   B. The doubling time of adenocarcinoma is 180 days.
   C. Small cell lung cancer is associated with paraneoplastic manifestations.
   D. In lung cancer, the spine and proximal long bones are rarely involved.
4. The following are true of lung cancer, except:
   A. The rate and growth of small cell lung cancer is early and rapid.
   B. Squamous cell lung cancer tends to cavitate and has a strong association with smoking.
   C. 80% of lung cancer is small cell carcinoma.
   D. Small cell carcinoma has poor prognosis and the 2-year survival rate is 5–8%.

MCQ Answers

1 = D; 2 = C; 3 = D; 4 = C

Short Answer Questions

1. List five paraneoplastic phenomena associated with lung cancer.
2. List five causes of solitary pulmonary nodule ("coin shadow").

SAQ Answers

1. (i) Hypercalcaemia; (ii) SIADH; (iii) Eaton-Lambert syndrome; (iv) Peripheral neuropathy; (v) Polymyositis
2. (i) Hamartoma; (ii) Sarcoidosis; (iii) Tuberculoma; (iv) Malignant; (v) Rheumatoid

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Pulmonary Embolism

12

Contents

Abstract

There is a marked discrepancy between the incidence of PE which is clinically diagnosed (1%) and autopsy findings in hospitalised patients (65%). This review highlights the improvements that have occurred in clinical care. Less than 30% of the PE is diagnosed on the index visit in the elderly. Restricted activity as in prolonged flights and prolonged rest or immobilisation and surgery pose enormous risk for developing deep vein thrombosis. In the elderly the diagnosis is often missed because of the non-specific and atypical presentation. The diagnosis of PE in the elderly is difficult because of the presence of cardiopulmonary comorbidities, and furthermore the characteristics of diagnostic tests for PE may be altered by age. A non-invasive diagnosis strategy combines clinical assessment, D-dimer estimation, ultrasonography and helical CT which yielded a diagnosis in 99% of outpatients suspected of PE.

Keywords

Pulmonary embolism · Deep vein thrombosis · D-dimer estimation · Helical CT · Computed tomography pulmonary angiography

Introduction

There is a marked discrepancy between the incidence of PE which is clinically diagnosed (1%) [1] and autopsy findings in hospitalised patients (65%) [2]. About 40% of PE found at necropsy of old patients were not suspected ante-mortem [3]. In the elderly population, the incidence of PE was 12.8% based on post-mortem studies over a 6-year period, and only one-third was diagnosed ante-mortem [4]. This accentuates the limitations of clinical diagnosis. PE is predominantly a disease of the elderly and is often underdiagnosed. The incidence of PE is increasing with the use of spiral CT scans (resulting in earlier diagnosis, with lower severity of illness and lower mortality), and these are due in all probability to early diagnosis [5]. The advent of

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_12

computed tomography pulmonary angiography (CTPA) has led to an increase in the incidence of PE diagnosis [6]. Less than 30% of the PE is diagnosed on the index visit in the elderly [7]. The incidence of thromboembolic events is greater in elderly men than women, whereas the incidence of PE is higher in women than in men younger than 55 years [8]. Accurate diagnosis is crucial because untreated in-hospital mortality is up to 30%, whereas with appropriate treatment, it is only 8% [9].

With the advent and availability of computed tomography scanners, considerable knowledge of the broncho-vascular anatomy is necessary to interpret the CT scans in the evaluation of PE. The main pulmonary artery (the pulmonary trunk) emerges from the right ventricle and at the level of the inferior margin of the carina bifurcates into the right and left pulmonary arteries [10]. The right pulmonary artery (RPA) originates at a right angle anterior to the left main bronchus and continues to the right hilum. The left (LPA) is more or less a continuation of the pulmonary trunk and heads towards the left hilum. Both RPA and LPA are ensheathed in the pericardium for a short distance from their origins. Once the respective pulmonary artery reaches the lung parenchyma, it divides up in tandem with the bronchial tree. The segmental arterial pattern somewhat follows the branches of the bronchial tree. Each lobar bronchus, segmental branches and lobular branches has a separate branch of the respective pulmonary artery.

Restricted activity as in prolonged flights and prolonged rest or immobilisation and surgery [11, 12] pose enormous risk for developing deep vein thrombosis. Bed rest, deep vein thrombosis of the lower limbs and venous insufficiency are the most common risk factors of PE [13]. In 65% of the patients, PE was associated with bed rest over 4 days, and 30% [14] to about 50% had DVT [15]. The incidence of pulmonary embolism increases with age. Heart diseases such as myocardial infarction, prosthetic cardiac valves, cardiomyopathies and atrial fibrillation are associated with increased risk of thrombosis. Cancer of the pancreas and myeloproliferative disorders like polycythaemia vera are well-known predisposing causes (Box 1). Genetic conditions with a propensity to venous thromboembolism are relatively rare, but these individuals have a high tendency for recurrence (Box 2).

Box 1 Risks and Predisposing Factors of Deep Vein Thrombosis

Prolonged Immobilisation
- Age
- Heart disease
- Malignancy
- Obesity
- Trauma
- Smoking
- Prothrombotic disorders

Box 2 Prothrombotic Disorders

Protein C and S
- Protein gene mutation (20210A)
- Factor V Leiden (activated protein C resistance)
- Homocysteine MTHFR mutation
- Fibrinogen level
- Factor XII deficiency
- Factor VIII

Clinical Manifestations

The typical presentation of PE with chest pain, sudden onset of dyspnoea, tachycardia and tachypnoea were most common [14]. In the elderly the diagnosis is often missed because of the non-specific and atypical presentation [16]. The Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) [17] study showed that symptoms may be mild, and generally recognised symptoms may be absent. Awareness of the likelihood of PE is foremost even in seemingly insignificant symptoms and signs and especially in patients with predisposing conditions and risk factors for venous thrombosis. Dyspnoea or tachypnoea occurred in 92% of the patients with pulmonary embolism in the

main and lobar pulmonary arteries, and the study revealed that dyspnoea and tachypnoea were less frequent in elderly patients with no previous cardiopulmonary disease [17]. Furthermore the study revealed dyspnoea, tachypnoea or pleuritic pain occurred in 92%, and one or more of these symptoms or signs of DVT were present in 98% of the patients. In all the three presentations, there was no prior heart or lung disease [17]. Dyspnoea may be absent in severe embolism and in patients with circulatory collapse. Syncope is a frequent presenting symptom in elderly patients with acute PE [18] and has a high in-hospital mortality [19].

Evaluation

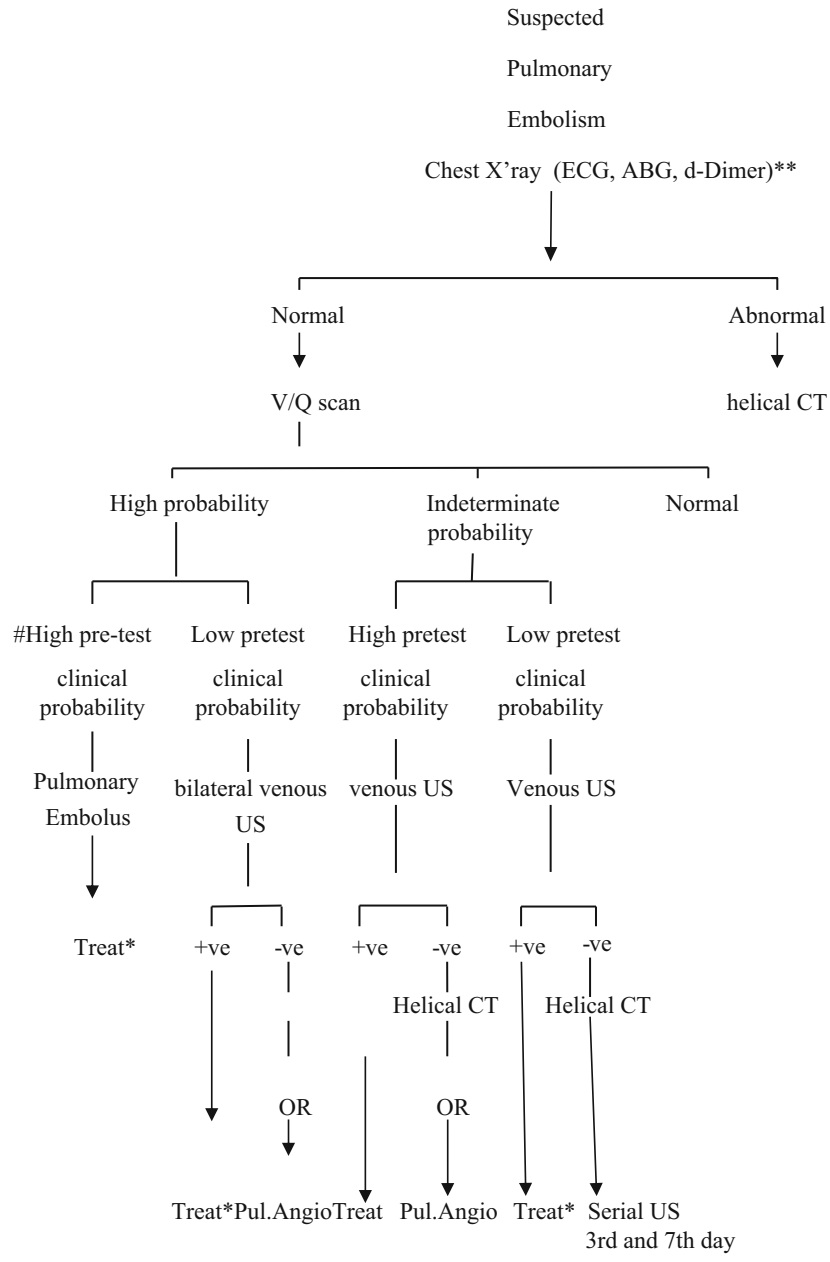
The characteristic symptoms and signs such as dyspnoea, chest pain, tachypnoea and hypotension are not specific for the diagnosis of PE. The diagnosis of PE in the elderly is difficult because of the presence of cardiopulmonary comorbidities, and furthermore the characteristics of diagnostic tests for PE may be altered by age [20]. PE poses an important diagnostic problem in patients with COPD. The two conditions show common symptoms of breathlessness, pleuritic pain, wheezing, haemoptysis and signs of right cardiac insufficiency [21]. PE in patients with COPD aggravates the already precarious respiratory state, and PE is a frequent factor of non-infectious respiratory decompensation in COPD patients [21]. The brain natriuretic peptide (BNP) and the N-terminal pro-brain natriuretic peptide (NT-proBNP) may predict adverse outcomes [22].

Clinical, instrumental and laboratory findings are non-specific, and a maintenance of a high level of suspicion is critical and can increase the likelihood of diagnosis [14]. PE should be suspected in the elderly at risk with unexplained dyspnoea, tachypnoea and tachycardia [16]. In the elderly validated diagnostic algorithms may have reduced applicability compared to the young [16]. The Wells predictive rate for diagnosing pulmonary embolism and deep vein thrombosis has been validated and is frequently used to estimate the probability of venous thromboembolism before performing more definite testing in patients [23]. In the elderly it does not perform that well as it does in younger patients, and physicians should use their clinical judgement in older patients and those with comorbidities [24]. The Wells pretest probability for pulmonary embolism categorises patients into low, moderate or high probability. It includes seven weighted variables: history of previous PE or DVT (1.5 points), heart rate >100 beats/min (1.5 points), recent surgery and immobilisation (1.5 points), clinical signs of DVT (3.0 points), alternate diagnosis less likely than PE (3.0 points), haemoptysis (1 point) and malignancy (1 point). A total score less than 2 is low probability, 2–6 medium and more than 6 high probability [23] (Box 3).

Box 3 Investigations in PE

Chest radiograph
- ECG
- D-dimer
- Arterial blood gases
- V/Q scan
- Duplex ultrasonography of legs
- Helical CT
- Pulmonary angiography

Chest X-ray findings are usually non-specific. The classical finding in PE is a wedged-shaped pleural-based opacity with apex directed towards the hilum (Hampton hump) [25]. Chest X-ray findings may indicate if V/Q scan or helical CT scanning should be the next step in the evaluation. PE can be confidently excluded with normal V/Q scan. Helical CT in the diagnosis of pulmonary embolism has been reported as having a wide range of sensitivities (66–93%) but a narrow range of summary specificities (89–98%) [26]. CTPA has improved the detection of life-threatening PE [27]; although it has been reported that subsegmental emboli can be missed on CTPA, their detection has improved with the availability of multi-detector screening (MDCT) [6, 25]. Whether these subsegmental filling defects are actually artefacts or whether they can be correlated with true subsegmental PE on pulmonary angiography is unclear [6]. CTPA may have



Information sources: Righini et al [20], Wells et al [23], Qaseem et al [24].

Fig. 1 Algorithm-suspected embolism. * Patients who show evidence of RV dysfunction and haemodynamic compromise are transferred to major centres. # Based on Wells clinical scoring system. ** (i) ECG: Usually non-specific. The S1Q3E# pattern and ST changes and right axis deviation seen only when there is severe right ventricular overload. (ii) Arterial blood gases, no single figure that can reliably establish or exclude PE. (iii) D-dimer, a quantitative D-dimer is reported to have a good negative predictive value; a positive test result is not useful, but a negative test result excludes PE [16]. Information sources: Righini et al. [20], Wells et al. [23], Qaseem et al. [24]

another drawback in that it may have led to overdiagnosis and overtreatment of clinically insignificant emboli [23]. CT pulmonary angiography (CTPA) has become the screening of choice especially when the chest X-ray is abnormal. It has a higher sensitivity and specificity than V/Q scan for the detection of PE. Furthermore it is preferred to V/Q scan in that the emboli can be visualised, the capability of obtaining a CT venogram in the same sitting and in patients with cardiopulmonary abnormalities and in excluding alternative pathology in the mediastinum or lung parenchyma [25]. Conventional pulmonary angiography is invasive, time consuming and less available, and the dye load may cause severe renal complications [25] and is rarely necessary [20]. A non-invasive diagnosis strategy combines clinical assessment, D-dimer estimation, ultrasonography and helical CT [20] which yielded a diagnosis in 99% of outpatients suspected of PE [28]. Figure 1 suggests an algorithm for the evaluation of and management of suspected pulmonary embolism.

All patients start with a chest radiography and a V/Q scan. Depending on the V/Q scan and the Wells pretest clinical probability results, the patients proceed to the next level in the evaluation. If the V/Q scan is normal, nothing further is done. Figure 1 shows the different levels in the evaluation. It is crucial to recognise, risk stratify and appropriately treat patients with acute severe PE. In patients with cardiopulmonary disease especially in the elderly with decreased functional reserve, there may occur a rapid onset of ventricular dysfunction compelling urgent and aggressive management [29]. An early risk stratification of patients with acute PE echocardiography is recommended by guidelines [30], and it is crucial to recognise promptly, risk stratify and befittingly treat patients with acute severe PE who will benefit from more aggressive therapy. Goldhaber [31] listed the following factors to be evaluated for a rapid and accurate risk stratification:

Firstly, a clinical evaluation for signs of right heart failure (elevated JVP, S3 gallop).

Secondly, bedside nonimaging tests – electrocardiogram and pulse oximetry (ECG, right ventricular strain pattern, with or without new right bundle branch block).

Thirdly, imaging tests – echocardiography (for moderate to severe RV dilatation and hypokinesis) and chest CT for right-left ventricular dimension ratio (a ratio of >0.9 in the reconstructed CT identifies an increased risk of death) [32].

Fourthly, cardiac biomarkers – troponins, B-type natriuretic peptide (BNP) and NT terminal proBNP [32].

Impact

In the elderly with acute pulmonary embolism (PE), the presentation is different to that of younger patients [33] and also unfavourably influence the characteristics of diagnostic tests [20]. These cause difficulties in diagnosis [34]. The incidence of PE increases steadily with age [34]. In elderly patients even when haemodynamically stable, PE is associated with high short-term mortality [35]. Because of the similarity in the clinical picture between PE and cardiovascular diseases such as congestive heart failure, pneumonia and COPD exacerbation, the diagnosis of PE can be challenging [36] (Box 4).

Box 4 Key Points. Acute Pulmonary Embolism

Less than 30% of the PE is diagnosed on the index visit in the elderly [7]. There is a bias based on age in that the elderly are not offered similar treatment to that of the younger patient.

The effects of the embolic thrombus will depend on a number of factors, namely, the size of the clot, the size of the affected pulmonary artery and the cardiopulmonary status of the individual [8].

The commonest cause of the pulmonary embolus is the thrombus which has

(*continued*)

Box 4 Key Points. Acute Pulmonary Embolism (continued)

originated from the popliteal vein or the larger veins above it.

In the elderly the diagnosis is often missed because of the non-specific and atypical presentation. The symptoms may be mild, and generally recognised symptoms may be absent [16, 17].

Accurate diagnosis is crucial; untreated in-hospital mortality is up to 30%, whereas with appropriate treatment, it is only 8% [9].

Awareness of the likelihood of PE is foremost especially in patients with predisposing conditions and risk factors for venous thrombosis.

An early risk stratification of patients with acute PE echocardiography is recommended by guidelines [30], and it is crucial to recognise promptly, risk stratify and befittingly treat patients with acute severe PE who will benefit from more aggressive therapy.

A non-invasive diagnosis strategy combines clinical assessment.

D-dimer estimation, ultrasonography and helical CT [20] yielded a diagnosis in 99% of outpatients suspected of PE [28].

Multiple Choice Questions

1. The following are true with pulmonary embolism (PE) in the elderly, *except*:
   A. Less than 30% of the PE diagnosed on the index visit in the elderly.
   B. The incidence of thromboembolic events is greater in elderly men than women, and the incidence of PE is higher in men than in women.
   C. Almost one-third of the patients with PE have DVT.
   D. Untreated in-hospital mortality is up to 30%, whereas with appropriate treatment, it is only 8%.
2. The following symptoms of PE in the elderly are true, *except*:
   A. Syncope is not a frequent presentation in elderly patients with acute PE.
   B. Symptoms may be mild and generally recognised symptoms may be absent.
   C. PE poses an important diagnostic problem in patients with COPD.
   D. The Wells predictive ratio for diagnosis of PE and DVT has been validated.
3. The following in relation to evaluation of PE are true, *except*:
   A. CT pulmonary angiography (CTPA) has become the screening of choice when chest X-ray is abnormal.
   B. If V/Q scan is normal or the probability is indeterminate, nothing further is done.
   C. The dye load in conventional pulmonary angiography may cause severe renal complications.
   D. The characteristic finding on chest X-ray is a wedged-shaped, pleural-based, triangular opacity with the apex directed towards the hilum.

MCQ Answers

1 = B; 2 = A; 3 = B

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Sleep Disorders

13

Contents

Abstract

The circadian rhythm is the major determinant of sleep and is regulated by an internal biological clock over a 24-h period. Insomnia is common in elderly people, and chronic insomnia is more common in this group. The changes in the sleep-wake patterns in insomnia have been attributed to the physiological changes that are part of normal ageing and age-related disturbances of the circadian sleep-wake rhythm. A careful sleep history is fundamental to the diagnosis and should include duration, quality, acceptable times (times of retiring and final morning awakening), frequency and duration of daytime naps. Careful assessment of environmental factors is necessary. The existence of medical and psychiatric conditions and primary sleep disorders such as sleep apnoea and neuromuscular dysfunctions should be identified, and the conditions addressed.

Keywords

Circadian rhythm · Insomnia · Hypnotics · Benzodiazepines

Introduction

The circadian rhythm is the major determinant of sleep and is regulated by an internal biological clock over a 24-h period [1]. The important factors which determine the amount and timing of sleep and sleep architecture (sleep stages) are the circadian rhythms, environment and time awake [2]. Two epidemiological studies found a high prevalence of insomnia in those over 60 years, especially among women [3]. However true sleep disorders are less prevalent in older people [4]. The elderly manifest early morning awakening, increased night-time wakefulness and increased fragmentation of sleep periods with corresponding decrease in total sleep time [5] that impedes daytime performance and optimal functioning. There are two distinct forms of sleep apnoea, obstructive (OAS) and central, and the former is more common. Disorders of partial arousal and those that interfere with sleep stage transitions are known as parasomnias. They occur during transition from wakefulness and NREM sleep or wakefulness and

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_8

REM sleep. Two sleep-related disorders, the restless leg syndrome (RLS) and the periodic limb movement disorder (PLMD), affect the elderly [6] with increasing severity.

Evaluation and Management

A careful sleep history is fundamental to the diagnosis and should include duration, quality, acceptable times (times of retiring and final morning awakening), frequency and duration of daytime naps. Excessive daytime sleep should be avoided and daytime naps restricted. About 50% of the elderly have insomnia; it is undertreated and nonpharmacological treatments are underused [7]. Careful assessment of environmental factors such as noise, light, temperature, bedding, etc., use of stimulants (caffeine, alcohol), use and misuse of sleeping tablets and social activity is necessary. The existence of medical and psychiatric conditions and primary sleep disorders such as sleep apnoea and neuromuscular dysfunctions should be identified, and the conditions addressed. The high prevalence of insomnia in the elderly is largely due to the frequent use of multiple medications together with medical and psychosocial comorbidities rather than ageing per se [8]. It is important to identify whether the insomnia is a primary or secondary condition [9]. In cases of suspected primary sleep disorders and sleep apnoea, specialist referral should be considered [10]. In mild and moderate insomnia, improved sleep hygiene will contribute to symptomatic relief [11].

Among the older people with sleep complaints, sleep maintenance rather than sleep initiation is the most common repetitive problem [12, 13]. According to Groulx [14] about one third of the patients who complain of difficulty in sleeping experience sleep patterns that are physiologically normal for their age. They require simple explanation and assurance. An additional third have problems related to underlying medical and psychiatric conditions which should be treated accordingly. The remaining third benefit from either behavioural modifications or medications [15]. The former teaches new sleep behaviours and ways to make the sleep environment more conducive to sleep. For most elderly, the short to immediate half-life benzodiazepines such as low-dose triazolam or temazepam are preferred [14]. The longer-acting agents have been shown to result in high risk of falls and hip fractures [15]. The newer non-benzodiazepine hypnotics, for instance, zaleplon and zopiclone, are very short acting with half-lives of 1 and 5 h, respectively. They have better side effect profiles, and zaleplon is effective at initiating sleep, whereas zopiclone is useful in patients with difficulty in falling asleep or staying asleep. Zaleplon does not appear to cause residual sedation or rebound insomnia [15]. Both these hypnotics tend to suppress slow-wave sleep (restorative aspect of sleep) less than the benzodiazepines [16].

Hypersomnias-Narcolepsy

Narcolepsy is a sleep disorder characterized by uncontrollable episodes of falling asleep during the daytime. The age of onset is between 15 and 30 years. In one review of 41 consecutive patients, 38% were in their 60s and 70s [17]. According to Atttarian [18], those that occur later are due to failure in recognizing the disease at an earlier age rather than late onset. Those that occur later in life are usually associated with Parkinson's disease or multiple sclerosis and are referred to as secondary narcolepsy [18]. All four symptoms are usually present in less than 50% of the cases.

Diagnosis

In the elderly especially, there is a delay in the diagnosis. Complicating matters are the elderly suffer from sleep problems associated with other physical and health effects of numerous medications they are usually on and normal age-related changes in sleep patterns [19, 20]. The excessive sleepiness in the elderly may be misjudged as attention-seeking or opting out behaviour, laziness, boredom or depression [21].

Treatment

Narcolepsy in the elderly may not need aggressive treatment [20] which has to be used with

caution. Stimulants such as Ritalin (methylphenidate) and Dexedrine (dextroamphetamine) have been approved for treatment. Others such as Provigil (modafinil) have been approved, but their effectiveness and safety have not been established [20].

Impact

The elderly manifest early morning awakening, increased night-time wakefulness and increased fragmentation of sleep periods with corresponding decrease in total sleep time that impedes daytime performance and optimal functioning. There is increased daytime sleepiness which affects the quality of life and has an effect on daytime activities [22] resulting in societal [23–25] and economic burden [26]. The total direct and indirect costs of insomnia were estimated between $30 and $35 billion annually [22]. A large proportion of the costs due to insomnia was attributed to common problems related to workplaces [25] such as work-related absences and reduced productivity [27]. Sleep disorders have been implicated with increased mortality [28] by affecting the quality of life not only due to excessive daytime sleepiness but also to physical, psychological and cognitive problems [29]. Sleep disorders may contribute to cognitive decline [30]. Other adverse effects include falls and aggravation of existing conditions such as heart disease and diabetes [23]. Poor sleep can have harmful outcomes in general well-being required for successful ageing [31], and poor subjective quality of sleep has been associated with risk of death by suicide during a 10-year period [32]. About half the number of elderly with sleep disorders are admitted to long-term care [33], and falls related injuries are significant factors for placement [29] (Box 1).

Box 1 Key Points: Sleep Disorders
The elderly manifest early morning awakening, increased night-time wakefulness and increased fragmentation of sleep periods with corresponding decrease in total sleep time [5].

There are two distinct forms of sleep apnoea, obstructive (OAS) and central, and the former is more common.

Disorders of partial arousal and those that interfere with sleep stage transitions are known as parasomnias. They occur during transition from wakefulness and NREM sleep or wakefulness and REM sleep.

Two sleep-related disorders, the restless leg syndrome (RLS) and the periodic limb movement disorder (PLMD), affect the elderly [6] with increasing severity.

Among the older people with sleep complaints, sleep maintenance rather than sleep initiation is the most common repetitive problem [12, 13].

According to Groulx [14], about one third of the patients who complain of difficulty in sleeping experience sleep patterns that are physiologically normal for their age.

For most elderly, the short to immediate half-life benzodiazepines such as low-dose triazolam or temazepam are preferred [14].

The longer-acting agents have been shown to result in high risk of falls and hip fractures [15].

Multiple Choice Questions

1. The following are true of narcolepsy except:
   A. Narcolepsy is uncontrollable episodes of falling asleep during daytime.
   B. Cataplexy, sleep waking and hypnagogic and hypnopompic hallucinations are associated with narcolepsy.
   C. It is associated with restless leg syndrome.
   D. When it occurs in late life, it is usually associated with diseases such as Parkinson' disease.
2. The following in relation to non-rapid eye movement (NREM) parasomnia are true except:
   A. Sleep walking

B. Bruxism
C. Uncontrollable episodes of falling asleep during daytime
D. Restless leg syndrome

MCQ Answers

1 = C; 2 = C

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Part III

Disorders of the Digestive Tract in the Elderly

Few gastrointestinal functions decline to any significant level as a result of old age. Nevertheless, in older people there is a decrease in the gastrointestinal reserves which make them extremely vulnerable to minor insults and decompensation can occur rapidly. Part III reviews the more common conditions in the elderly such as dysphagia, gastroesophageal reflux disease, peptic ulcer, colorectal cancer, inflammatory bowel disease, and infectious diarrhea. There are two main subcategories of dysphagia namely oropharyngeal dysphagia and esophageal dysphagia involving different phases of swallowing. Esophageal motility disorders usually present with dysphagia and chest pain and associated with a variety of abnormal manometric abnormalities. GORD is caused by failure of the lower esophageal sphincter (LES). The greatest concern with GORD is the development of complications. Barrett's esophagus is common in the middle-aged and the elderly. Worldwide the incidence of peptic ulcer disease and their bleeding complications are increasing in the old-aged population. The main cause of peptic ulcers is *Helicobacter pylori* infection. Peptic ulcer disease is a huge burden on health-care economics. The prevailing belief is that colorectal cancer is the result of accumulation of both mutations and epigenetic modifications of several genes. Colorectal cancer causes considerable physical and psychological morbidity. The inflammatory bowel diseases (IBD) – ulcerative colitis (UC) and Crohn's disease (CD) – are chronic progressive and debilitating diseases associated with substantial impact on the daily lives of affected individuals. A number of medications are available such as corticosteroids (oral and topical), 5-aminosalicylates, immunomodulators, antibiotics, and biological agents. GI bleeding is associated with higher rates of hospitalization, increased morbidity and mortality in the elderly than in the young, and is a common medical emergency. Abdominal pain can be due to many causes and the underlying pathology could be due to an infection, mechanical obstruction, biliary disease, malignancy, and gastrointestinal ischemia. *Clostridium difficile* is the most common cause of nosocomial diarrhea and remains a disease of the elderly.

The Oesophagus and Oesophageal Disorders

14

Contents

Abstract

The three main symptoms of oesophageal disease or disorder are dysphagia, noncardiac chest pain and heartburn. Oropharyngeal dysphagia and oesophageal dysphagia often present as a symptom of a larger disease process and are a secondary diagnosis. Stroke is a leading cause of oropharyngeal dysphagia. Oesophageal dysphagia is caused by disordered motility or is a result of obstruction to the passage of the food bolus through the oesophagus to the stomach. Oesophageal dysphagia is basically due to either motility disorders (primary or secondary) or to mechanical obstruction (intrinsic or extrinsic). The prevalence of gastro-oesophageal reflux disease (GORD) increases with age and the elderly are more likely to develop severe disease. The greatest concern with GORD is the development of complications. Barrett's oesophagus is common in the middle-aged and the elderly. The primary

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_20

goal in the management of GORD is to promote the healing of the damaged oesophagus, by suppression of acid secretion, alleviating the symptoms, and preventing complications. The review summarises the main group of oesophageal disorders with the main focus on their effects and/or adverse effects.

Keywords
Oropharyngeal dysphagia · Oesophageal dysphagia · Gastro-oesophageal reflux disease · Proton-pump inhibitors (PPI)

Introduction

Normal swallowing is divided into three phases, namely, oral phase, pharyngeal phase and oesophageal phase. The basic mechanisms that make up swallowing are bolus preparation, lubrication, oral delivery, closure of the palate, closure of the airway, pharyngeal propulsion and upper oesophageal sphincter opening [1].

Oral phase includes oral preparation. In this phase, the food is chewed mixed with saliva and made into a bolus. The back of the tongue is raised to keep the bolus in the oral cavity. The duration of this portion of the oral phase varies [2, 3]. The prepared bolus is transported from the anterior to the posterior oral cavity. The posterior part of the tongue is retracted and raised against the hard palate [3]. The oral phase is voluntary and ends when the bolus passes the anterior faucial pillars and touches the pharyngeal wall, and the tongue forces the bolus into the pharynx. This part of the oral phase lasts between 0.7 and 1.2 s [4].

During the pharyngeal phase, the bolus is voluntarily pushed upwards and backwards into the oropharynx by the tongue. The larynx ascends and moves forwards by the pull of the suprahyoid muscles. The palatopharyngeal muscles partially close the mouth from the pharynx so as to prevent the bolus sliding back into the mouth. Once in the oropharynx, the mechanism is involuntary. This phase lasts for about a second. The soft palate is elevated blocking off the nasopharynx, and laryngeal closure begins from bottom up and the epiglottis moves over the laryngeal opening protesting the airway [2, 3]. The pharyngeal phase lasts for about 0.6 s [4]. This phase involves the motor and sensory tracts of the cranial nerves IX and X. The larynx lowers and the cricopharyngeal muscle contracts to prevent reflux.

Oesophageal phase begins with the bolus being carried by peristalsis through the oesophagus with some help from gravity towards the cardiac sphincter. The cardiac sphincter relaxes in response to muscle contractions of the oesophagus and swallowing and remains relaxed till the food bolus is propelled into the stomach. This is under the control of the brainstem (medulla) and the myenteric plexus. This phase usually lasts 8–20 s but is slower in the elderly [2, 3].

Oesophageal Disorders

The four main symptoms of oesophageal disease or disorder are dysphagia, noncardiac chest pain, heartburn [5] and regurgitation. About 2–5% of patients seen in the emergency department have noncardiac chest pain (NCCP) [6]. Population studies estimate the prevalence of NCCP as ranging between 19.5% and 33% [7, 8]. Using symptom-based descriptions, the prevalence of heartburn and regurgitation was found to be 19.8% over a 1-year period [9]. In a longitudinal study of GORD with heartburn as a cardinal symptom, Kotzam et al. [10] found an incidence of 5.4 per 1,000 persons.

Oral abnormalities including difficulty ingesting, controlling and delivering bolus relative to swallowing initiation were seen in 63% [11]. Pharyngeal dysfunction consisting of bolus retention and lingual propulsion or pharyngeal constrictor paralysis was seen in 29%. Thirty-nine percent showed pharyngoesophageal segment abnormalities; mostly cricopharyngeal muscle dysfunction and minor abnormalities of oesophageal function were seen in 36% [11]. Deficits in neurological function caused by true central nervous system degenerative processes and cerebrovascular accidents have to be

differentiated from age-related changes [12] and can be difficult.

Oropharyngeal dysphagia and oesophageal dysphagia often present as a symptom of a larger disease process and are a secondary diagnosis.

Oropharyngeal Dysphagia

Oropharyngeal dysphagia results from disturbances in the oropharyngeal physiology such as poor tongue movement in chewing, reduced peristalsis in the pharynx, reduced laryngeal elevation or closure and cricopharyngeal dysfunction [13]. The dysphagia in the elderly is most often oropharyngeal, and the common basis for oropharyngeal dysphagia in the elderly is neurological disease [14] especially stroke [15], Parkinson's disease and advanced dementia among others or, to obstructive lesions, tumours, Zenker's diverticulum, anterior mediastinal masses and external structural lesions. Exacerbation of COPD is a significant presentation of patients with oro-oesophageal disorders [16].

Neuromuscular Disorders

In pseudobulbar palsy, the muscles of swallowing and talking controlled by the lower cranial nerves, IX, X and XII, are bilaterally impaired, and is the result of an upper motor lesion involving the corticobulbar pathways in the pyramidal tract. Examples are bilateral hemispheric infarction, multiple sclerosis, motor neurone disease and high brainstem tumours [17].

Bulbar palsy refers to bilateral impairment of function of the lower cranial nerves IX, X and XII which occurs due to lower motor neurone lesion either at the nuclear level or in the medulla or from bilateral lesions of the lower cranial nerves outside the brainstem. Examples are medullary infarction, motor neurone disease, syringobulbia, Guillain-Barre syndrome, poliomyelitis, Lyme disease and brainstem tumours [17].

Stroke is a leading cause of oropharyngeal dysphagia [15] and affects 37–45% using cursory techniques, 51–55% with clinical testing and 64–78% with instrumental testing [18]. A third of the patients with stroke are admitted to rehabilitation [19]. Bilateral corticobulbar tract damage or a brainstem lesion is usually considered to be the cause of the dysphagia in stroke. But it is known to occur in stroke resulting in unilateral hemispheric lesions but is prominent brainstem stroke [18]. Some of the victims recover soon from the swallowing disorder, while others do not (Table 1).

Infective and inflammatory disorders – Guillain-Barre syndrome is a rapidly progressive form of inflammatory polyneuropathy. In the severe form of the disease, more than half the patients have weakness of the oropharyngeal and facial muscles.

Insidious Onset

Motor neurone disease – Amyotrophic lateral sclerosis is a rapidly progressive disease where speech and swallowing disorders parallel each other. Parkinson's disease is a progressive disorder and affects 1% of the population above the age of 50 years. Multiple sclerosis has a variable presentation, and dysphagia occurs in the pharyngeal phase of swallowing. In myasthenia gravis, the difficulty in swallowing occurs towards the end of the meals. In primary muscle disorders, the dystrophies of the dysphagia can result from spasm of the superior constrictor muscles or the cricopharyngeal muscles. In several of the autoimmune disorders such as systemic sclerosis, systemic lupus erythematosus, dermatomyositis and Sjogren's and mixed connective tissue disorders, there is a high incidence of dysphagia.

Obstructive Oropharyngeal Dysphagia

Causes include neoplastic processes involving the nasopharynx, Zenker's diverticulum and pharyngeal diverticulum that arises from the posterior hypopharynx above the cricopharyngeal muscle. Most individuals with a diagnosis of Zenker's diverticulum are in the sixth to eighth decades of life [20]. Oropharyngeal dysphagia is a common presentation. And a crepitus may be felt in the neck. Oesophageal webs are most frequent in the hypopharynx.

Table 1 Distinguishing features between pseudobulbar and bulbar palsies

	Pseudobulbar palsy	Bulbar palsy
Dysphagia	Dysphagia	Nasal regurgitation
Labile effect	Yes	Difficulty in chewing
		Choking on liquids
		No
Speech	Slow, thick	Nasal
Gag reflex	Normal or exaggerated	Absent
Tongue	Small, stiff, spastic	Wasted, fasciculations
Jaw jerk	Brisk	Normal or absent
Other neurological deficits	UMN lesions of limbs	LMN lesions of limbs

Laryngopharyngeal Reflux(LPR)

LPR is the result of upper oesophageal sphincter dysfunction. In a study of 113 patients with laryngeal and voice disorders, 50% of the entire study population had pH-documented reflux [21]. Compared to white patients, the prevalence of pH-documented LPR was low in the Chinese [22]. There is a high incidence of LPR in patients with head and neck cancer [23]. Otolaryngologists have identified 4–10% with symptoms and signs consistent with reflux [24, 25]. LPR results from backflow of gastric contents (acid and pepsin) resulting in mucosal damage [26, 27] into the larynx and pharynx.

Symptomatology

Patients often have a burning sensation in the throat with excessive clearing of the throat, persistent cough and hoarseness. Other symptoms may include feeling of lump in the throat, sensation of postnasal drip and trouble swallowing. Examination may reveal posterior laryngitis. There is no burning sensation in the lower chest as in GORD**.**

Oesophageal Dysphagia

Oesophageal dysphagia is caused by disordered motility or as a result of obstruction to the passage of the food bolus through the oesophagus to the stomach [15]. Oesophageal dysphagia is basically due to either motility disorders (primary or secondary) [28] or to mechanical obstruction (intrinsic or extrinsic) [15] (Table 2).

Table 2 Causes of oesophageal dysphagia

I Motility disorders
I. Primary
Achalasia
Diffuse oesophageal spasm
'Nutcracker oesophagus'
Non-specific oesophageal motility dysfunction
Hypertensive lower oesophageal sphincter
II Secondary
Scleroderma and other connective tissue disorders
Chagas' disease
Diabetes mellitus
Chronic idiopathic intestinal pseudo-obstruction
Neuromuscular disorders of striated muscle
II Obstructive (mechanical)
I Intrinsic
Benign and malignant tumours
Oesophageal webs
Oesophageal diverticula
Peptic strictures
Lower oesophageal (Schatzki's) ring
Foreign bodies
II Extrinsic
Mediastinal abnormalities
Compressed by vascular structures
Cervical osteoarthritis

Information sources: [31], [33], [36], [63], [64], [70], [71]

Primary Motility Disorders

Oesophageal motility disorders usually present with dysphagia and chest pain [29] and associated with a variety of abnormal manometric abnormalities [30].

I. *Achalasia* is a disease of oesophageal motility [31] and is characterised by incomplete relaxation of the cardiac sphincter and reduced peristalsis in the mid- and lower oesophagus and increased lower oesophageal sphincter pressure. It results from degeneration of the myenteric plexus of the oesophagus [32] leading to denervation of the oesophageal muscle.

The onset is insidious and progressive with dysphagia for both liquids and solids. Other symptoms may include regurgitation of undigested food and nocturnal cough. Although usually painless in some, it may resemble diffuse oesophageal spasm with substernal pain. There is progressive dilatation of the oesophagus. Respiratory complications include cough and aspiration pneumonitis and in long-standing cases weight loss and evidence of malnutrition. A very unusual complication is oesophageal cancer [29].

Diagnosis is confirmed by barium swallow which shows dilatation of the oesophagus with a smooth tapered narrowing of the distal end resembling a 'bird beak' [29] and or by oesophageal manometry. Endoscopy should be performed to rule out carcinoma at the distal end, and there is increased resistance to the passage of the endoscope at the cardia.

II. *Diffuse oesophageal spasm* (*DES*) is more appropriate to describe as distal oesophageal spasm37 and is characterised by replacement of normal peristalsis by phasic nonpropulsive contractions. It is found in less than 5% of the patients undergoing oesophageal motility testing [33]. Intermittent dysphagia for solids and liquids often accompanied by chest pain [34] may resemble angina. The pain is variable and is often precipitated by foods or hot or cold beverages. However it may occur spontaneously and in the absence of dysphagia may be confused with angina. Over many years it may evolve into achalasia for in some cases malfunction of the lower oesophageal sphincter occurs. Barium X-rays show nonpropulsive contractions giving the appearance of a corkscrew. Oesophageal manometry provides the most sensitive test. Edrophonium injected during oesophageal manometry can provoke contractions [35].

Nutcracker oesophagus (*NE*) is characterised by oesophageal contractions that are coordinated but with an excessive amplitude. Food can generally pass down the oesophagus, but pain is common [36]. It can affect all age groups, but it is more common in the elderly, and it occurs more in women than in men [36]; prevalence is rising.

Gastro-oesophageal Reflux Disease (GORD)

The prevalence of GORD in the western world is 10–20% [37, 38] and is less in Asia [39], and the prevalence in urban population from Northern India is 16.2%, similar to other industrial countries [40]. In a survey in the UK, 28.7% of the respondents had GORD symptoms of either heartburn or acid regurgitation on more than six occasions in the previous year [41]. The prevalence of GORD increases with age and the elderly are more likely to develop severe disease.

In the elderly, age-related changes such decreased salivary secretions, reduced or loss of lower oesophageal sphincter tone, diminished oesophageal motility and gastric acid hypersecretion may lead to GORD. The 'classical' GORD is referred to as erosive GORD. A non-erosive or negative endoscopy reflux disease is now recognised (NERD) and constitutes about 60% of all GORD [41] (Box 1).

Box 1 Predisposing Factors

Hiatus hernia
- Obesity
- Smoking
- Excessive alcohol ingestion
- High levels of caffeine consumption
- Drugs
- Family history

Symptomatology

Classical symptoms of GORD are heartburn, acid regurgitation [41, 42], noncardiac chest pain and some difficulty in swallowing and burning feeling originating in the region of the stomach or lower chest and ascending up to the neck. It is often aggravated by large meals especially at night or by meals high in fat. In others it is brought about by recumbency or exercise. Regurgitated material is tasted in the mouth and swallowed back. Many experience high epigastric and substernal pain and globus sensation in 25–50% of cases [43]. Pain on swallowing and excessive salivation are less common. Other extraoesophageal symptoms include chronic cough, laryngitis, asthma, sinusitis, erosion of dental enamel, dental hypersensitivity and damaged teeth [44]. GORD was the third leading cause of chronic cough after sinus conditions and aspiration accounting for 21% of cases [45]. Compared to the young and adult patients, the symptoms of GORD are different in the elderly, and oesophagitis is more severe [46].

The greatest concern with GORD is the development of complications. Barrett's oesophagus is common in the middle-aged and the elderly. There is replacement of the normal squamous epithelium by columnar epithelium or intestinal metaplasia of the oesophageal mucosa. Peptic strictures and peptic ulcers may develop and malignant transformation may arise from the metaplastic columnar epithelium. It presents as dysphagia from the oesophageal stricture or less commonly bleeding from the oesophageal ulcer. Heartburn is often absent.

Diagnosis

A detailed history is vital and a high degree of suspicion is necessary to make a diagnosis [46]. Investigations include barium swallow X-ray, response to omeprazole, oesophageal manometry, oesophagogastroduodenoscopy (EGD) and 24 h oesophageal pH monitoring. The response to treatment with PPI is as sensitive as 24 h pH monitoring in the diagnosis of GORD. Endoscopy is required for patients with alarming symptoms, new or persistent symptoms (Box 2). According to the Gastroenterological Society of Australia (GESA) [48], endoscopy should be reserved for the following (see Box 3).

Box 2 Alarm symptoms

Age >55 years
- Family history of upper GI cancer
- Unexplained weight loss
- New-onset dyspepsia
- GI bleeding
- Dysphagia
- Odynophagia
- Unexplained iron deficiency anaemia
- Persistent vomiting
- Information sources: De Vault [47].

Box 3 GESA *guidelines for endoscopy

Alarm symptoms
- Diagnostic uncertainty
- Symptoms not responding to initial treatment
- Long-standing troublesome symptoms
- Symptoms in older people especially Asian population
- Preoperative assessment
- To detect and manage Barrett's oesophagitis
- Reassure when anxiety persists about diagnosis
- *Gastroenterological Society of Australia [48]

Oesophagoscopy provides accurate diagnosis of oesophagitis with or without haemorrhage. There are several classifications of the severity of the oesophagitis. The Los Angeles classification describes four grades of oesophagitis severity based on the oesophageal lesions referred to as mucosal breaks [49]. However, it does not describe in detail the features of severe or complicated oesophagitis. The MUSE (M, metaplasia; U, ulceration; S, stricture; and E, erosion) system overcomes this and provides clear descriptions of the endoscopic findings [50].

Treatment

The primary goal in the management of GORD is to promote the healing of the damaged oesophagus, by suppression acid secretion, alleviating the symptoms and preventing complications and to improve [51]. The management of GORD requires a combination of lifestyle changes, pharmacological measures and occasionally surgery in selected patients [52]. A vast number of the patients can be symptom controlled at the self-care and primary care levels that include posturing (avoiding slouching, lying on the left side, lying down with head elevated) and size and timing of meals among others.

The lifestyle changes which includes cessation of smoking; avoidance of alcohol, caffeine and chocolate; weight reduction; and avoidance of large and late and fatty meals should be integrated at all stages and from the very beginning when therapy begins. Majority of the patients require pharmacological therapy, and this varies according to the severity of symptoms [53]. There are a number of drugs used in the management of GORD, the over-the-counter drugs (antacids, alginic acid and gastric H_2 receptor blockers), prokinetic drugs and the proton-pump inhibitors (PPI). Most of the patients respond to general measures and simple antacids if GORD is mild. The antacids and alginics do not change the underlying amount of acid secretion nor prevent complications and hence are used as a temporary measure in the treatment of mild symptoms. The different drugs in the class of H_2 receptor blockers vary slightly in their potencies and onset of action. In the elderly, PPIs are more effective in healing and reducing oesophagitis compared to H2 blockers.

The PPIs are considered the most effective and safe in the short term [54] and should be used in all cases except perhaps if the disease is mild. The PPIs omeprazole, pantoprazole and lansoprazole and the new-generation PPIs, esomeprazole and rabeprazole, are widely used for the treatment of GORD [55]. The first-generation PPIs do not achieve a sustained suppression of acid secretion [56]. There are differences in the hepatic metabolism of these drugs – variability of acid suppression, drug interactions and possibly clinical efficacy [54, 55]. Several studies have shown that PPIs effectively heal erosive oesophagitis at 8 weeks with an efficacy of 80% or greater [57, 58, 59]. PPIs have also been shown to be more effective than H2 receptor blockers in relieving symptoms and mucosal healing [60] and produce faster and more complete symptom relief [50]. For severe GORD, continuous maintenance therapy with PPIs is the standard of care [53], but some may respond to intermittent short courses [53] (Table 3).

Several professional organisations have produced guidelines for the diagnosis and management of GORD – the American Gastroenterological Association Institute [61], Gastroenterological Society of Australia [48], American College of Gastroenterology, the Gstaad Guidelines and NICE. The updated Gstaad new algorithm separated care levels into self, primary and secondary. In the vast majority of patients, the reflux of the symptoms can be controlled at self- and primary care levels [61].

Based on these guidelines, an algorithm for the management of GORD is presented (Fig. 1). There are two approaches to managing GORD, 'step-up' and 'step-down'. The principles of 'step-up' and 'step-down' are often driven by cost considerations. 'Step-up' therapy starts with antacids + lifestyle modifications and if symptoms are not controlled and if there is no response to a PPI, an H_2 antagonist is given. In the case of 'step-down' therapy, PPI and subsequently an H_2 antagonist are given once symptoms are controlled. With 'step-up' therapy, the initial costs are low and avoid overtreatment, but the patient may continue to have symptoms. With 'step-down' therapy, there is higher initial cost, but there is rapid symptom relief. In a randomised open-label pilot study with omeprazole, the investigators found that 'step-down' approach gave a statistically significant increase in the clinical effectiveness compared to 'step-up' compared with 'step-up' approach in terms of relief of symptoms [62]. However, there is no clear evidence to endorse either treatment strategy [44].

Table 3 Pharmacotherapy in GORD

Drug and brand names	Mechanism of action	Adverse effects
I.Proton-pump inhibitors (PPI)		
Omeprazole-*Losec,Omez* Pantoprazole- *Somac, Pantazol* Lansoprazole-*Zoton, Levant*	Blocks irreversibly the H+/K+ ATPase enzyme system of the gastric parietal cells- acting at the source of acid production Do not have rapid or sustained suppression	common to all PPI -gastrointestinal -nausea, dairrhoea, abdominal pain less commonly- anxiety, depression long term-hypomagnaesmia, *C difficile* infection
Second generation Esomeprazole-*Nexium Esoto* Dexalamsoprazole-*Kapidex* Rabeprazole- Pariet, *Rebol*	similar properties as above plus lower oxidative hepatic metabolism rate decreased rate of drug interactions, possibly better efficiency	lower risk of drug-drug interactions
II. Gastro H_2 –receptor blockers		
Cimetidine- *Tagamet* Famotidine- *Pepcidine* Ranitidine-Zantac Nizatidine- *Tazac*	Blocks the histamine receptor in the parietal cells inhibiting basal gastric secretion	Gastrointestinal disturbance; altered liver function tests headache, dizziness, constipation, diarrhoea skin rashes, interacts with alcohol; potential drug reactions with cimetidine
III. Antacids	neutralizes gastric acid thereby reducing acidity	
Calcium salts -*calcium carbonate* Aluminium salts		GI upset, acid rebound Milk-alkali syndrome (high doses) constipation,accumulates in
-Aluminium hyroxide Magnesium salts		renal impairment, hypophosphotaemia diarrhoea,accumulares with renal impairment
Sodium bicarbonate		Milk-alkali syndrome in high doses
IV. Alginic acid -*Gaviscon*	forms a thick gel coating on surface of stomach contents -preventing them from refluxing into the oesphagus	diarrhoea,nausea, vomiting
V.Prokinetic agents		
Metoclopromide	Increase gastric emptying and lowers oesophageal sphincter	neurological- extrapyramidal effects; -tardive dyskinesia
Domepromide		hypoprolactaemia,gynecomastia. extrapyramidal effects
VI. Sucralfate -*Carafate*	Forms a viscous like paste capable of acting as an acid buffer	constipation, flatulence, xerostomia bezoar formation

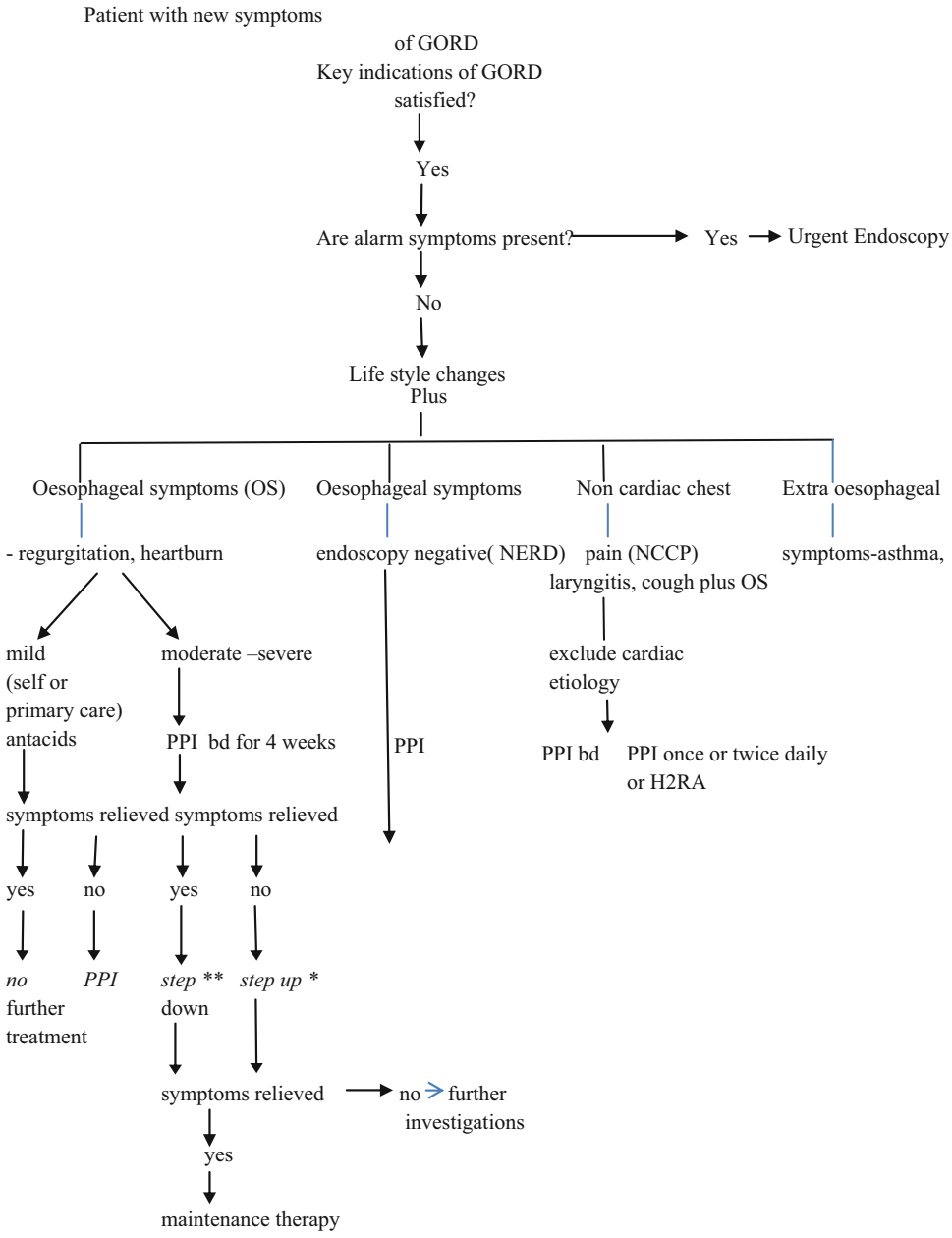

Fig. 1 Management of GORD

Secondary Motility Disorders

Apart from the primary motility disorders which are more infrequent, the secondary motility disturbances are associated with neuromuscular diseases; connective tissue disorders and endocrine disorders are more common in the elderly and in patients with multiple morbidities [63]. Secondary oesophageal motility disorders can be caused by Chagas' disease, scleroderma and other connective tissue disorders, chronic idiopathic pseudo-obstruction, diabetes mellitus, myxoedema, alcoholism and multiple sclerosis.

I. Scleroderma. Occasionally patients with scleroderma and in some instances with systemic lupus erythematosus do exhibit swallowing problems which are posture related. It can be demonstrated by swallowing in the recumbent position. In scleroderma dysphagia is caused initially by impaired oesophageal motility but later can result from gastro-oesophageal reflux and secondary stricture formation.
II. Chagas' disease is caused by infection with *Trypanosoma cruzi* which is characterised by cardiomyopathy and megaoesophagus or megacolon. It is found in South America. About one-third of the patients develop dilatation at different locations in the gastrointestinal tract such as megaoesophagus and megacolon [64]. This is caused by enteric nervous system injury by *T. cruzi* [65].

Obstructive (Mechanical)

Patients with mechanical obstruction complain of difficulties in swallowing during the transport of solid food down the oesophagus once it has passed the upper oesophageal sphincter.

Oesophageal carcinoma is one of the most common cancers in the world, and there is a wide geographical variation in its prevalence. About 90% of the oesophageal cancers are squamous carcinoma, but adenocarcinoma of the lower end of the oesophagus and stomach cardia is increasing [66]. In Australia oesophageal cancer represents 1.2% of all causes and is responsible for 2.1% of cancer deaths [67]. Most patients with adenocarcinoma of the distal oesophagus would have had Barrett's oesophagus which is the result of chronic gastro-oesophageal reflux and reflux oesophagitis. In Barrett's oesophagus, the squamous epithelium of the distal oesophagus is replaced by glandular and columnar mucosa [68].

It usually presents with dysphagia [67, 69] for solids more than liquids with weight loss and occasionally gastrointestinal bleeding may be the first presentation. Physical examination reveals generalised wasting together with pallor due to anaemia and supraclavicular or cervical lymphadenopathy. It can metastasise to the liver, lung and other sites. Compression of the sympathetic will give rise to Horner's syndrome, and involvement of the recurrent laryngeal may lead to vocal cord paralysis and hoarseness of voice.

Barium studies will demonstrate the obstructive lesion; endoscopy provides for diagnostic biopsy and CT scan to determine the extensiveness of the disease. An elevated alkaline phosphatase and transaminase levels may indicate metastasis to the liver. Complications include aspiration, oesophageal obstruction, bleeding and spread to the mediastinum. The prognosis is poor, and most patients die within 4–12 months of the diagnosis, and 5-year survival is less than 10%.

Peptic stricture. GORD causes chronic inflammation at the distal end of the oesophagus resulting in a stricture, referred to as peptic stricture. Patients with peptic stricture would have had symptoms over several years and an end stage of chronic oesophageal reflux [70]. These patients often present with dysphagia for solids and later to liquids as well. Other symptoms include regurgitation, weight loss and heartburn. The heartburn may improve as the stricture occurs which then acts as a barrier to reflux.

Schatzki's ring. The lumen in the lower one-third of the oesophagus becomes narrowed by a ringlike anatomical structure and is located in the squamocolumnar mucosal junction. It is a common cause of intermittent dysphagia depending on the size of the lumen and difficulty with some foods, for example, large boluses of bread or meat. Barium studies can demonstrate the ring provided the distal oesophagus is adequately dilated.

Diverticula of the Oesophagus

Most oesophageal diverticula occur in middle-aged adults and the elderly. Diverticulum in the distal oesophagus (epiphrenic) usually presents with dysphagia, regurgitation, pain [71] and aspiration. Epiphrenic diverticulum occurs just above the diaphragm and is often associated with achalasia. Mid-oesophageal diverticulum (traction) is

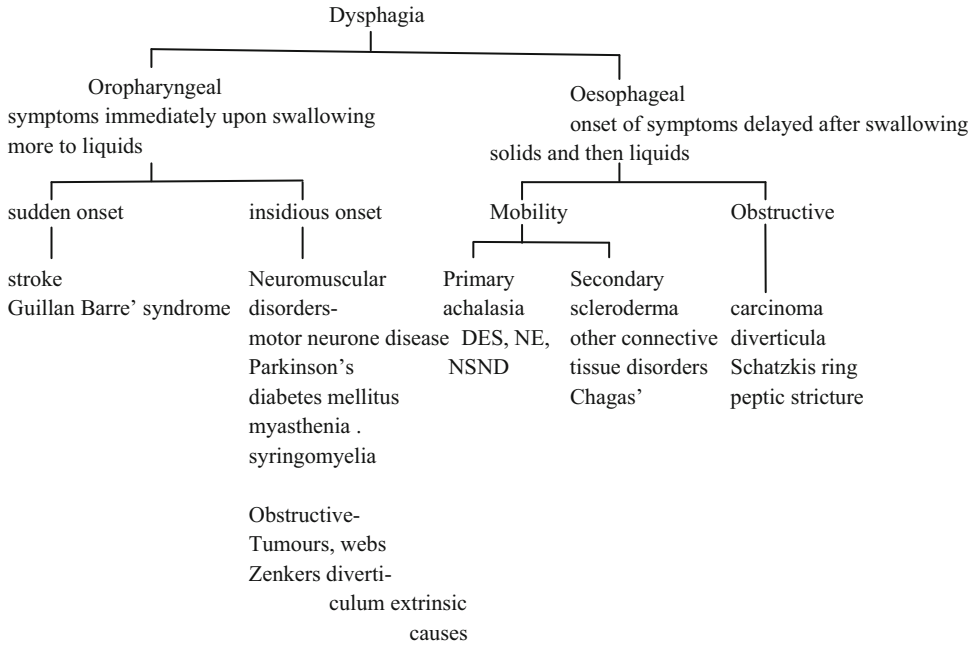

Fig. 2 Differential diagnosis of dysphagia

often associated with oesophageal spasm or mediastinal fibrosis.

Differential Diagnosis of Dysphagia

See Fig. 2.

Evaluation of Dysphagia

A good history usually indicates the underlying cause in about 80% of the cases [72] together with physical examination. Possible causes of angina-like chest pain after excluding cardiac diseases are GORD and spastic motility disorders of the oesophagus [63]. To begin with videofluoroscopy is used in evaluating oropharyngeal dysphagia [15, 72]. Barium oesophagography identifies most anatomic causes of dysphagia and cine-oesophagoscopy useful to provide clues to possible motor disorder causing dysphagia [15, 73]. In the case of a suspicion of an obstruction or gastro-oesophageal reflux disease, endoscopy is the best choice [15]. When a motor disorder is suspected, oesophageal manometry is indicated [73].

Impact

A large European observational study found that GERD was associated with substantial impact on daily lives of affected individuals in a primary care setting [74]. This is most striking in areas of pain, mental health and social function [75]. The impairment of HR-QoL in patients affected is proportional to the frequency and severity of heartburn which is greater than that associated with many other chronic diseases [76]. Other factors which may worsen HR-QoL are being female, nocturnal symptoms and increased body mass index [77]. GERD affects all three components of QoL, namely, physical, social and psychological satisfying the consensus definition of QoL provided by the WHO in 1948 [78]. HR-QoL is significantly impaired in GERD [77] compared to the general population [75]. Several studies have demonstrated that treatment improves QoL [75, 79, 80] (Box 4).

Box 4 Key Points: Oesophageal Disorders

The four main symptoms of oesophageal disease or disorder are dysphagia, non-cardiac chest pain, heartburn[5] and regurgitation [5].

Oropharyngeal dysphagia and oesophageal dysphagia often present as a symptom of a larger disease process and is a secondary diagnosis.

The dysphagia in the elderly is most often oropharyngeal, and the common basis for oropharyngeal dysphagia in the elderly is neurological disease [14] especially stroke [15], Parkinson's disease and advanced dementia among others or obstructive lesions, tumours, Zenker's diverticulum, anterior mediastinal masses and external structural lesions.

Oesophageal motility disorders usually present with dysphagia and chest pain [29] and associated with a variety of abnormal manometric abnormalities [30].

Associated with a variety of abnormal manometric abnormalities: achalasia [31], diffuse oesophageal spasm (DES) [33], nutcracker oesophagus (NE) [36] and gastro-oesophageal reflux disease (GORD) [37, 38] among others.

Compared to the young and adult patients, the symptoms of GORD are different in the elderly, and oesophagitis is more severe [46].

The greatest concern with GORD is the development of complications.

The management of GORD requires a combination of lifestyle changes, pharmacological measures and occasionally surgery. Vast number of the patients can be symptom controlled at the self-care and primary care levels.

The primary care physician should make known self-care measures – changes to lifestyle including posturing (avoid slouching, lying on the left side, lying down with head elevated), meal size and meal timings among others.

Box 4 Key Points: Oesophageal Disorders (continued)

The PPIs are considered the most effective [54] and should be used in all cases except perhaps if the disease is mild.

The PPIs omeprazole, pantoprazole and lansoprazole and the new-generation PPIs, esomeprazole and rabeprazole, are widely used for the treatment of GORD [55].

Multiple Choice Questions

1. The following statements in relation to swallowing are true *except*:
   A. In oropharyngeal dysphagia, symptoms come on immediately upon swallowing liquids.
   B. In severe form of Guillain-Barre syndrome, more than half have weakness of the oropharyngeal and facial muscles.
   C. In motor neurone, disease is a rapidly progressive disease where speech and swallowing parallel each other.
   D. In laryngopharyngeal reflux, there is severe heartburn.
2. The following is true of pseudobulbar palsy *except*:
   A. Pseudobulbar palsy is the result of an upper motor lesion involving the corticobulbar pathways in the pyramidal tract.
   B. Manifests as dysphagia and the speech is slow and thick.
   C. The tongue is wasted and there are fasciculations.
   D. The jaw jerk is brisk.
3. The following are true of oesophageal cancer *except*:
   A. About 90% of the oesophageal cancers are squamous cell carcinoma.
   B. Most patients with adenocarcinoma of the distal oesophagus would have Barrett's oesophagus.
   C. It usually presents with dysphagia for liquids more than for solids with weight loss.
   D. Endoscopy provides for a diagnostic biopsy.

4. The following in relation to gastro-oesophageal reflux disorder (GORD) are true *except*:
   A. Heartburn is the most common complaint of the elderly with GORD.
   B. The elderly with GORD are more likely to develop serious disease.
   C. Endoscopy is the gold standard for evaluation.
   D. Effective way of treating GORD is by eating frequent large meals.

MCQ Answers

1 = D; 2 = C; 3 = C; 4 = D

Short Answer Questions

1. List 4 extraoesophageal symptoms of gastro-oesophageal reflux disorder (GORD).
2. List 4 complications of oesophageal carcinoma.

SAQ Answers

1. Chronic cough; asthma; laryngitis; erosion of dental enamel.
2. Aspiration; oesophageal obstruction;spread to mediastinum; bleeding

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Peptic Ulcer Disease in the Elderly

15

Contents

Abstract

The prevalence of *H. pylori* increases with age [81], and the prevalence of *H. pylori* infection in patients with peptic ulcer has been reported to range from 58% to 78% in patients aged over 65 years. In the old-aged population worldwide, the incidence of peptic ulcer disease and their bleeding complications are increasing. Peptic ulcer disease is associated with hyperfunction of the G cell, increased gastric secretion and pepsinogen, impaired bicarbonate secretion and the presence of inflammatory indicators. There is strong evidence that smoking, regular use of aspirin and prolonged use of steroids are associated with the development of peptic ulcers.

Keywords

H. pylori infection · Peptic ulcer disease · Gastrointestinal bleeding · Proton-pump inhibitor [PPI] · Cigarette smoking

Introduction

The prevalence of *H. pylori* increases with age [1], and the prevalence of *H. pylori* infection in patients with peptic ulcer has been reported to range from 58% to 78% in patients aged over 65 years [2]. In the old-aged population worldwide, the incidence of peptic ulcer disease and their bleeding complications are increasing [3]. Although the prevalence of *H. pylori* is falling, the elderly remain at risk for peptic ulcer because of the widespread use of NSAIDs [4]. The male/female ratio in peptic ulcer is 4:1. Duodenal ulcer is four times as common as gastric ulcer [5]. Duodenal ulcer is two to three times more common in first-degree relatives, and there is an increased risk of getting gastric ulcer in relatives of gastric ulcer patients [5]. Patients with blood groups A and O are more prone to *H. pylori* infection and AB group less prone [6], and individuals with blood group O have a higher risk of peptic ulcers [7].

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_17

Peptic ulcer disease is associated with hyperfunction of the G cell, increased gastric secretion and pepsinogen, impaired bicarbonate secretion and the presence of inflammatory indicators [8]. In the elderly decreased secretion of gastric secretions and impairment of mucous-bicarbonate barrier may lead to gastric ulcer [9].

Investigations

(i) Faecal occult blood; (ii) CBC, LFT, amylase and lipase; (iii) *H. pylori* can be diagnosed by non-invasive techniques such as urea breath test, blood test, stool antigen assay and invasive techniques such as rapid urease test on antral biopsies, culture, histological examination [10] and polymerase chain reaction (PCR) [11]. The biopsy site has to be carefully selected in elderly patients. The 13C-urea test has a higher accuracy than serology in the elderly for monitoring after treatment. To detect *H. pylori*'s DNA in gastric mucosa, saliva and dental plaques, PCR methods are the best option [11]. Upper GI endoscopy in any patient 50 years or over with new onset of symptoms.

Treatment Plan

H. pylori Positive

There is strong evidence that smoking, regular use of aspirin and prolonged use of steroids are associated with the development of peptic ulcers [5]. The following factors are associated with increased risk of bleeding in NSAID users: co-morbidities, corticosteroid, anticoagulant co-therapy, peptic ulcer or recent bleeding and alcoholic consumption. Cigarette smoking should cease and alcohol imbibed in moderation. There are no dietary restrictions unless certain foods are associated with problems. Stress should be reduced.

Medications: Proton-pump inhibitor [PPI] + clarithromycin + amoxicillin (PPI: omeprazole, lansoprazole, rabeprazole, esomeprazole). Triple therapy for 10–14 days is considered the treatment of choice. The treatment regimes are omeprazole, amoxicillin and clarithromycin (OAC) for 10 days and lansoprazole, amoxicillin and clarithromycin (LAC) for either 10 or 14 days. LAC compared to lansoprazole, amoxicillin and levofloxacin is used as a first-line therapy [12].

Goal: complete elimination of *H. pylori*.

Retest for efficacy: urea breath test no sooner than 4 weeks after therapy to avoid false negatives.

Stool antigen test: an 8-week interval should be allowed after therapy.

H. pylori-negative patients: evaluate after 1 month.

List of major antiulcer drugs:

H2 receptor antagonists – tidine
Proton-pump inhibitors – prazole
Surface-active agents – sucralfate
PGI-1 analogs – misoprostol
Bismuth compounds

H2 receptor antagonists inhibit H2 receptors of gastric parietal cells ➔ leading to decrease in release of HCl. Proton-pump inhibitors-diffuse into the parietal cell and inhibit the effect of the H+/K+ ATPase pump. This means H+ cannot efflux out of the cell and inhibits 50–90% of acid. Sucralfate acts as a binder. Misoprostol binds to the EP3 receptor decreasing HCl production and promoting mucous and bicarb secretion. Bismuth compounds increase bicarbonate mucous production and may bind to ulcer site.

Impact

Peptic ulcer disease is a huge burden on healthcare economics in the United States. The annual healthcare costs have been estimated at nearly $6 billion, as one in ten Americans during their lifetime suffers from peptic ulcer disease [13]. In a longitudinal study, the investigators found the QoL of patients with chronic gastritis was lower than that of patients with peptic ulcer disease and was lower than in the population norms [14]. QoL in both groups were associated with risk factors

that differed by age and gender. The greatest concern with GORD is the development of complications. Barrett's oesophagus is common in the middle-aged and the elderly, level of education and marriage [14]. As age advances the adverse effects diminish with prevention of *H. pylori* or ulcer cure [15] (Box 1).

Box 1 Key Points: Peptic Ulcer Disease

In the elderly decreased secretion of gastric secretions and impairment of mucous-bicarbonate barrier may lead to gastric ulcer [9].

There is strong evidence that smoking, regular use of aspirin and prolonged use of steroids are associated with the development of peptic ulcers [5].

H. pylori can be diagnosed by non-invasive techniques such as urea breath test, blood test, stool antigen assay and invasive techniques such as rapid urease test on antral biopsies, culture, histological examination [10] and polymerase chain reaction (PCR) [11].

Triple therapy for 14 days is considered the treatment of choice with *H. pylori*-positive patients.

Multiple Choice Questions

1. The following are true of peptic ulcer *except*:
   A. Duodenal ulcer is more common with blood group O.
   B. The male/female ratio is 1:4.
   C. Duodenal ulcer is three times more common in first-degree relatives.
   D. Gastric ulcer is more related to *H. pylori* than duodenal ulcer.
2. The following are true of peptic ulcer *except*:
   A. The increased amounts of acid damage the duodenum resulting in the formation of duodenal ulcers.
   B. Cigarette smoking and *H. pylori* are cofactors for the formation of peptic ulcer disease.
   C. The prevalence of peptic ulcer is unrelated to the socio-economic status.
   D. The lifetime prevalence of developing ulcer disease in first-degree relatives of ulcer patients is three times greater than in the general population.
3. The following are true of peptic ulcer disease *except*:
   A. *H. pylori* is effectively eradicated by a combination of PPI and antibiotics.
   B. *H. pylori* and NSAID therapy are the most prevalent factors involved in peptic ulcer bleeding.
   C. In patients with previous bleeding, switching to selective COX-2 inhibitors concomitant PPI therapy is not needed.
   D. The elderly remain at risk of peptic ulcer because of the widespread use of NSAIDs.
4. The following are true of peptic ulcer disease *except*:
   A. Serology has a significantly higher accuracy than the 13C-urea breath test in the elderly.
   B. Upper GI bleeding carries a high mortality rate especially in the elderly.
   C. Retest for efficacy – urea breath test no sooner than 4 weeks after therapy to avoid false negatives.
   D. Retest for efficacy – an 8-week interval should be allowed after therapy with stool antigen test.
5. The following are true of the actions of drugs used in peptic ulcer *except*:
   A. Proton-pump inhibitors inhibit the effect of the H+/K+ ATPase pump and inhibit 50–90% of acid.
   B. Bismuth compounds decreases bicarbonate mucous production.
   C. H2 receptor antagonists inhibit H2 receptors of the gastric parietal cells leading to decreased release of HCl.
   D. Misoprostol binds to the EP3 receptor decreasing HCl production and promoting mucous and bicarb secretion.

MCQ Answers

1 = B; 2 = C; 3 = C; 4 = A; 5 = B

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Colorectal Cancer

16

Contents

Abstract

The cause of colorectal cancer is not understood and appears to involve interactions between inherited susceptibility and environmental factors. Environmental factors play an important role and can increase the risk of colon cancer. The symptoms of colorectal cancer are similar to that of many other bowel disorders, but early colon cancer is asymptomatic. The risk of developing colorectal cancer rises sharply after the age of 40 years. A person under 40 years with positive family history should be investigated. It is appropriate to perform one or all the following in the order to make a firm diagnosis.

Keywords

Colorectal cancer · Western diet · Familial adenomatosis · Polyposis

Introduction

Data from cancer registers show that in 2001, colorectal cancer was the most common newly diagnosed cancer with 12,844 new cases of bowel or colorectal cancer reported [1]. According to the Australian Bureau of Statistics the common causes of cancer deaths were breast (6%), lung (15%), colorectal (12%) and lymphoid and related tissues (10%) [2]. Colorectal cancer is the second leading cause of death in the United States [3, 4] and approximately 60,000 die each year [5]. It is common in Italy and throughout Europe with about 250,000 cases each year [6]. There are racial and ethnic disparities, in incidence, mortality and survival rates [3]. The age-adjusted incidence rates are higher in Alaskan men followed by the Japanese and African American men and mortality rates highest for African Americans [3].

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_15

The cause of colorectal cancer is not understood and appears to involve interactions between inherited susceptibility and environmental factors. CRC develops through a series of genetic changes [7] by way of a progressive multistep process resulting from accumulation of genetic mutations especially involving the Wnt signalling pathway [8]. The prevailing belief is that CRC is the result accumulation of both mutations and epigenetic modifications of several genes [9]. Over the past two decades because of our better understanding of the molecular pathogenesis of CRC, it has become apparent that epigenetic changes have important roles in the pathogenesis of CRC [8, 9, 10]. Epigenetic regulation is constituted at several levels involving primarily DNA methylation [8, 9]. Environmental factors play an important role and can increase the risk of colon cancer [6]. Western diet (particularly one rich in red meat, high fat and low vegetables) is a predisposition [4].

Symptoms and Signs

The symptoms of colorectal cancer are similar to that of many other bowel disorders, but early colon cancer is asymptomatic. There was an unexplained change in bowel habits, especially a recent one, bleeding from rectum often occult, lower abdominal pain of recent onset, loss of weight, persistent feeling of fullness and anaemia. The individual may be pale, abdomen may be distended and mass felt, and evidence of loss of weight, hepatomegaly (metastatic disease) and digital rectal examination may reveal a mass or blood.

Risk Factors and Risk Stratification

The risk of developing colorectal cancer rises sharply after the age of 40 years, and one in 21 - Australians is likely to die of colorectal cancer during his or her lifetime [11]. Before the age of 75, the lifetime risk is one in 17 for males and one in 26 for females with incidence of mortality progressively increasing with age [12]. In addition to FAP and HNPCC, colon cancer occurs commonly in clusters in families [12]. The extent of the risk will depend on the degree of kinship and the age of disease of the index case. When the first-degree relative is affected and the risk of colon cancer is two to threefold [12, 13] and if multiple first-degree relatives have colon cancer or the age with diagnosis of cancer made in the relative is the age of 50 years, the risk is further increased [14]. In an individual with a history of a first-degree relative with colon cancer, colon screening is recommended starting at the age of 40 years [13]. When two first-degree relatives are affected with colon cancer or one first-degree relative is diagnosed under the age of 55 years, colonoscopy at an age 10 years younger than the age of CRC [13] or colonoscopy every 5 years is recommended [13, 15]. It is essential to recognise patients who are at intermediate risk and provide them with appropriate screening recommendations [13]. In potentially high-risk patients with multiple (two to three or more) first-degree relatives on the same side diagnosed with CRC, or one first- or second-degree relative with suspected FAP, or someone in the family with APC or proven HNPCC families, annual or two-yearly colonoscopy is recommended [15]. If there is no family history of CRC or ulcerative colitis or first-degree or second-degree relative with CRC diagnosed after 55 years, FOBT every 2 years after 50 years is recommended [15] (Box 1).

Box 1 Risk Factors for Colorectal Cancer

Genetic: hereditary non-polyposis
Colorectal cancer (HNPCC)
Familial adenomatous
Polyposis (FAP)
Colorectal adenomas
Chronic ulcerative colitis
Crohn's disease
High-fat, low-fibre diet

Differential Diagnosis and Diagnosis

Differential diagnosis includes inflammatory bowel disease, diverticular disease, mesenteric ischaemia, solitary rectal ulcer and arteriovenous malformations. A patient over the age of 40 with

recent onset of symptoms or signs warrants investigations. A person under 40 years with positive family history should be investigated. It is appropriate to perform one or all the following in the order to make a firm diagnosis. Screening includes digital rectal examination, home faecal occult blood testing (FOBT), flexible sigmoidoscopy, colonoscopy [16] or air contrast barium enema (DCBE). In older patients because of the frequency of colonic lesions and inability to appraise histology, colonoscopy is preferred to barium enema. Although colonoscopy remains the most accurate screening test for CRC at a single exercise, more recently CT colonography (CTC) studies have established that colonoscopy can miss polyps and may also miss CRC [17]. Colonoscopy relies on the expertise of the operator. With CTC the whole bowel can be visualised and localise any lesion identified, but the radiation burden can be high especially where it has to be repeated regularly [18].

Faecal Occult Blood Test (FOBT)

Several studies have shown that population-based screening programmes using FOBT with people over 50 years can reduce bowel cancer deaths by 30–40% among those who do the test [19, 20]. There are two types of FOBT: guaiac (chemical-CFOBT) and immunological (I-FOBT). The latter has many advantages and is currently recommended [21]. A few days before the test, the patient should change his diet and also stop taking certain medications. It must be remembered that a negative FOBT does not exclude the presence of cancer. If positive, further tests are required, colonoscopy. Extraction of DNA from the stool is now feasible and has shown high sensitivity for CRC, and it has been recommended that FOBT should be used with the DNA markers to increase the sensitivity further [16]. Some of the commonly investigated mutations are APC [22], BRAF [23], K-ras [24], BAT-26 [25] and more recently markers of hypermethylation [26].

The disease is staged (Dukes' classification) into stage A, confined to mucosa/submucosa; stage B, invasion of the muscularis propria; stage C, involving the local lymph glands; and stage D, spread beyond the bowel and lymph glands. A 5-year survival rate based on Dukes' classification is 93% for Dukes' stage A, 77% for stage B, 48% for stage C and 9% for stage D [27]. Since survival rate improves with early detection, considerable effort is made to screen individuals with no symptoms as well as those with one or more symptoms. In the early stages, the survival rate is about 90%, and only about 9% less than half are found in stage 1 (Dukes' A) [27].

Impact

Colorectal cancer (CRC) causes considerable physical and psychological morbidity [28]. When faced with the diagnosis of CRC, the QoL of patients and family becomes intensely transformed [29]. To evaluate the full impact of CRC on patients and family, it would be necessary to understand the QoL experienced by patients [28]. Those who survive following full treatment have psychosocial issues such as cancer-related distress, adaptations to physical changes and difficulties related to return to work [30]. The complexities relating to the impact of CRC patients and their families place a huge burden on health care [31]. Ceilleinchair et al. [32] examined the economic impact of CRC and found it to be built around three related costs, namely, costs related to health services, employment and patient and families all adding up to social costs. There will be substantial impact upon the expenditure and cost effect if CRC could be prevented or detected early. It has been reported that by increasing the uptake of CRC screening in the United States to 80% by 2018, there would be a significant public health impact by preventing approximately 280,00 new cancer cases and 200,000 cases of death with less than 20 years [33]. The Australian Program found that there may be a meaningful impact on CRC diagnosis and an expected improvement in survival [34]. Since survival rate improves with early detection, considerable effort is made to screen individuals with no symptoms as well as those with one or more symptoms (Box 2).

Box 2 Key Points. Colorectal Cancer

Colorectal cancer is the second leading cause of death in the United States [3, 4] and approximately 60,000 die each year [5].

There are racial and ethnic disparities, in incidence, mortality and survival rates [3].

Genetic factors are important. Familial risk of colon cancer is common.

Western diet (particularly one rich in red meat, high fat and low vegetables) is a predisposition [4].

In an individual with a history of a first-degree relative with colon cancer, colon screening is recommended starting at the age of 40 years [13]. When two first-degree relatives are affected with colon cancer or one first-degree relative is diagnosed under the age of 55 years, colonoscopy at an age 10 years younger than the age of CRC [13] or colonoscopy every 5 years is recommended [13, 15].

Screening includes digital rectal examination, home faecal occult blood testing (FOBT), flexible sigmoidoscopy, colonoscopy [16] or air contrast barium enema (DCBE).

With CTC, the whole bowel can be visualised and localise any lesion identified, but the radiation burden can be high especially where it has to be repeated regularly [18].

Multiple Choice Questions

1. The following in relation to colorectal cancer is true except:
   A. Fifteen to 20% have a family history of colorectal cancer without genetic predisposition.
   B. Calcium increased risk of colon cancer in the elderly.
   C. Nutritional intervention has been identified as an important part in its prevention.
   D. Screening tests should be done before symptoms appear.
2. It is appropriate to perform the following in order to make a diagnosis except:
   A. Digital rectal examination and sigmoidoscopy.
   B. A negative FOBT does not exclude the presence of colon cancer.
   C. In elderly patients barium enema is preferred to colonoscopy.
   D. In the early stages, the survival rate is about 90% and less than half are found in this stage.

MCQ Answers

1 = B; 2 = C

Short Answer Questions

1. List four risk factors for colorectal cancer

SAQ Answers

1. Family history
2. high-fat low-fibre diet
3. colorectal adenomas
4. chronic ulcerative colitis

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Inflammatory Bowel Disease in the Elderly

17

Contents

Abstract

Inflammatory bowel disease (IBD) embraces two diseases, Crohn's disease (CD) and ulcerative colitis (UC), which are immunologically mediated, chronic, relapsing and inflammatory conditions of unknown aetiology. In the elderly, there are two groups, elderly with onset of IBD at a later age (late onset) and, the other, elderly with a long-standing history of IBD with an initial diagnosis at a younger age. Late-onset CD has been variably defined ranging from 40 to >65 years of age. The review summarises the two diseases, Crohn's and ulcerative colitis, with the main focus on the age of onset.

Keywords

Crohn's disease (CD) · Ulcerative colitis · Inflammatory bowel disease · Late-onset CD · Late-onset ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) embraces two diseases, Crohn's disease (CD) and ulcerative colitis (UC), which are immunologically mediated, chronic, relapsing and inflammatory conditions of unknown aetiology [1]. It occurs worldwide with a continuing increase in the incidence [2] especially in the developing countries [3]. The prevalence of Crohn's disease and ulcerative colitis is highest in Europe [4] and North America but remains rare in Eastern Europe [5]. Recent studies have shown steep increases in IBD in Hungary and Croatia [3]. About 1.4 million Americans have been diagnosed with IBD and up to 16% have been diagnosed at 60 years or older [6]. It is becoming prominent in Asian countries and Asian migrants in Western countries [7]. There is a disparity between the West and East, and this is attributed to a difference in Western

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_16

lifestyles [8, 9]. IBD has a racial-ethnic distribution and Jewish population is highly susceptible [136]. With ageing of the population, IBD has become a growing problem in the elderly [10] and 10–30% of the IBD population are above the age of 60 years, and 10–15% of the cases of IBD are diagnosed in patients 60 years and over [10]. The Crohn's disease has its peak onset in early life and a second peak among the elderly [11], and a third of the newly diagnosed occurs in the elderly with twice the number of females [12, 13].

Clinical Manifestations

In the elderly, there are two groups, elderly with onset of IBD at a later age (late onset) and, the other, elderly with a long-standing history of IBD with an initial diagnosis at a younger age [10]. Late-onset UC has been variably defined as >50 years to >70 years [14]. Late-onset CD has been variably defined ranging from 40 to >65 years of age [14]. In the elderly compared to the young, the presentation is not significantly different [14]. First flare occurs in 10% of the IBD patients over the age of 60 years, and there is a similar distribution between UC and CD and the younger age groups [15]. In UC diarrhoea, rectal bleeding and severity of the symptoms are less harsh in older group [16, 17]. In the older age group, fever and loss of weight are significantly less common [18]. In a study of Crohn's disease made after the age of 50 years, the common presenting signs and symptoms were in the order of abdominal pain being the commonest, followed by diarrhoea, weight loss and bleeding from the gastrointestinal tract [19, 20]. In the older patient, the distal ileum is the commonest site, and the presentation is acute after initially mild symptoms [21].

UC and CD have different patterns of involvement differing in their location, distribution, depth of involvement and histology [22]. In UC patients >60 years old, left-sided involvement and proctitis were more common than in younger patients according to the Montreal classification [10, 15, 23]. In Crohn's disease, the most common site of involvement is in the distal ileum (47.4%), followed by large bowel (36.6%) and both large and small in 16% in the elderly [18]. In another study, the ileum was involved in 54%, the colon in 25% and ileocolon in 20.8% [24]. Others have found left-sided lesion in predominantly elderly women with Crohn's disease [25, 26], and colonic CD is usually confined to the distal or left colon [21].

With regard to disease behaviour with CD, inflammatory behaviour, stricturing, penetrating disease and perianal involvement were similar in incidence compared to younger patients with stricturing being the commonest in both [24]. Hadithi et al. [27] in their study found that 17% of the patients over the age of 60 years with IBD had extraintestinal manifestations which included peripheral arthritis, uveitis, spondylitis and erythema nodosum. Other manifestations include pyoderma gangrenosum, oral aphthous ulcers, episcleritis, uveitis and sclerosing cholangitis [28]. The incidence of extraintestinal IBD manifestations is no different from that of younger patients, although a disparity exists with some reports [18, 29, 30].

Differential Diagnosis and Diagnosis

In elderly patients, there are a number of clinical situations that may impede the diagnosis of IBD. In the elderly, IBD may be complicated by diverticular disease, ischaemic colitis, cancer or infections [14] or certain medications such as NSAIDs and antibiotics [31, 32]. These can mimic IBD on radiologic, endoscopic or histologic testing [31]. IBD is often misdiagnosed or overlooked due to the comorbidity in the elderly [33]. Atypical manifestations are common in the elderly with IBD and can give rise to difficulty in diagnosis [34]. Diverticulosis is present in more than half the patients older than 60 years, and segmental colitis with diverticulitis (SCAD) requires special attention [35, 36] often masquerading as IBD [37]. The diagnosis of IBD in the elderly is often delayed, 6 years compared to 2 years in young patients [37].

Management and Prognosis

Treatment selection in UC and CD will largely be determined by the location, extent, severity and disease behaviour [38, 39]. The burden of comorbidities in the elderly patient with IBD is best gauged by distinguishing the frail from fit elderly [40] as opposed to categorizing them solely on age [41]. The indications for medical and surgical therapy in elderly patients are similar to that of younger patients [30]; although there has been significant progress for such therapy, they pose additional challenges in the elderly [34]. The treatment options are similar to that of younger patients, but potential side effects and pharmacological interactions must receive due consideration [15]. A number of medications are available such as corticosteroids (oral and topical), 5-aminosalicylates, immunomodulators, antibiotics and biological agents. In mild to moderate flare of UC, oral and/or mesalazine is the main option [15], but the efficacy of mesalazine in CD is uncertain, and it has a restricted role in mild flares in CD of ileal or colonic location [39, 42]. Mesalazine combined with beclomethasone has been shown to be effective in moderate flares of left UC when given as a single 5 mg dose for 2–4 weeks with remissions occurring in about 60% of the patients [43]. The conventional immunomodulatory agents used are methotrexate, mercaptopurine and azathioprine. With regard to the use of biological agents, the indications are similar to that of patients below the age of 60 years, but one of the significant feature is the their safety profile especially those related to infection [15]. A number of biologics targeting specific immunological pathways have been studied [44, 45]. Infliximab, a TNF antagonist, is used in UC. In a study of 66 patients over the age of 65 years on anti-TNF therapy versus 112 younger patients, elderly anti-TNF recipients had lower clinical response rate at 10 weeks (68% vs 89%) but not at 6 months, and their risk of adverse events was higher [46]. Other TNF antagonists such as adalimumab and golimumab have shown significant effectiveness [47]. Other biological agents with different mechanisms, vedolizumab, an integrin receptor antagonist, and tofacitinib, a Janus kinase inhibitor, are appearing as new medications [47]. Randomised trials have shown that vedolizumab is effective in the treatment of UC and CD [48]. In a retrospective study of 102 patients with UC in the context of sustained remission discontinued thiopurines, an analysis of the outcomes showed that the overall relapse rate was 32.5% with relapse rates of 18.88% at 1 year and 43.04% at 5 years [49]. Faecal markers such as calprotectin or lactoferrin are useful in the diagnosis of IBD [50, 51], for non-invasive monitoring of disease activity [50–54] and predicting response to treatment and relapse [50] of UC patients. Faecal calprotectin correlates better with endoscopic disease activity than clinical activity with C-reactive protein, ESR, platelets and haemoglobin [52, 53].

Surgery

In the elderly, failure of medical treatment is the commonest indication for surgery [15], and the elderly CD have more perioperative complications and higher mortality rates [55]. In UC, restorative proctocolectomy with ileal pouch-anal anastomosis is the surgical technique of choice [56], and age is not a contraindication [15]. UC in the elderly is less severe with fewer relapses and hospitalisations compared to CD [24]. In the elderly with Crohn's disease, distal colonic involvement is common and carries a good prognosis except those with perforation [57]. In the elderly, there is a higher mortality rate after the initial attack and often related to the co-morbidities [41]. In elderly patients, the disease course is more severe, and in both UC and CD, the mortality of hospitalised patients is about three to five times higher than in the group below 65 years [15].

Impact

The inflammatory bowel diseases (IBD) – ulcerative colitis (UC) and Crohn's disease (CD) – are chronic, progressive and debilitating associated with substantial impact on the daily lives of

affected individuals. Patients with UC experience decrements in QoL in terms of general health perception [58]. Psychological functioning is an important factor [58–60]; anxiety and depression [58], unemployment/work and sick leave [61] are associated with poor QoL. Studies have shown that active treatment improves QoL in UC patients to levels comparable to the general population [62, 63]. UC patients overall report better HR-QoL than CD patients [64]. Another important factor in the decline of HR-QoL is disease activity [58, 65, 66]. The survival rates following colectomy in 10 years after diagnosis are 4–10% in recent studies [67]. UC patients live with endless and variable symptoms where a flare-up results in social isolation [68]. The impact of UC manifolds in physical symptoms, emotional factors and social consequences and intervention. Patients with UC currently have normal life expectancy [9]; however, they have an increased risk of colorectal cancer [69] and cholangiocarcinoma [70] (Box 1).

Box 1 Key Points: Inflammatory Bowel Disorders

With ageing of the population, IBD has become a growing problem in the elderly [10].

The Crohn's disease has its peak onset in early life and a second peak among the elderly [11], and a third of the newly diagnosed occurs in the elderly with twice the number of females [12, 13].

UC and CD in spite of their immunological and clinical differences share part of their cytokine profile and display elevated levels of TNF-alpha [22].

In the older age group with UC, fever and loss of weight are significantly less common [18].

In the older patient with CD, distal ileus is the commonest site and the presentation is acute after initially mild symptoms [21].

Treatment selection in UC and CD will largely be determined by the location, extent, severity and disease behaviour [38, 39].

Box 1 Key Points: Inflammatory Bowel Disorders (continued)

The treatment options are similar to that of younger patients, but potential side effects and pharmacological interactions must receive due consideration [15].

Faecal markers such as calprotectin or lactoferrin are useful in the diagnosis of IBD [50, 51], for non-invasive monitoring of disease activity [50–54] and for predicting response to treatment and relapse [50] of UC patients.

Multiple Choice Questions

1. The following are true of ulcerative colitis (UC), except:
   A. The severity of the symptoms is less harsh in the late-onset UC.
   B. Fever and weight loss are less common in the late onset.
   C. Left-sided and proctitis are less common in UC patients older than 0 years.
   D. Late-onset CD has been variably defined ranging from 40 years to >65 years of age
2. The following are true of UC and Crohn's disease (CD), except:
   A. UC and CD have similar patterns of involvement differing in their location, distribution, depth of involvement and histology.
   B. Colonic CD is usually not confined to the distal or left colon.
   C. The common presenting signs and symptoms of Crohn's disease after the age of 50 years are abdominal pain followed by diarrhoea, weight loss and bleeding from the gastrointestinal tract.
   D. The Crohn's disease has its peak onset in early life and a second peak among the elderly.
3. The following are true of inflammatory bowel disease (IBD), except:
   A. Faecal markers such as calprotectin or lactoferrin are useful in the diagnosis of IBD.
   B. Faecal calprotectin correlates poorly with endoscopic disease activity than clinical

activity with C-reactive protein, ESR, platelets and haemoglobin.

C. Randomised trials have shown that vedolizumab is effective in the treatment of UC and CD.

D. Atypical manifestations are common in the elderly with IBD and can give rise to difficulty in diagnosis.

MCQ Answers

1 = C; 2 = B; 3 = B

Case Study

Crohn's disease in an 88-year-old male – an unusual presentation

Presentation: An 88-year-old asymptomatic male on routine laboratory studies had a haemoglobin of 126 g/L. Six months earlier, it reaches 139 g/L, and the ferritin level was from 61 to 27 ug/L. He was not on any medications such as NSAIDs. Faecal occult blood tests were positive. Colonoscopy revealed no lesions in the colon other than diverticula. There were five to six ulcers in the distal ileum and unable to say whether there were ulcers higher up. CT enteroclysis was followed by the 'pill' scan. The latter revealed several small erosions in the duodenum and multiple aphthous and small ulcerations in mid- to distal bowel with normal mucosa in between (Fig. 1). Other tests such as ANCA, ANSA and CRP QuantiFERON GOLD were normal. High levels of IgG to antibodies to *Saccharomyces cerevisiae* with high levels of IgG were detected. It was suggested that in all probability it was Crohn's disease although biopsy was not done. He was treated with budesonide (9a corticosteroid) 3 mg bid for 8 weeks. A repeat 3 months later showed a haemoglobin of 134 g/L and ferritin of 43 ug/L, and there was no recurrence 12 months later.

Comment: Anaemia in IBD is complex. Determining ferritin concentration with serum transferrin receptor gives a reliable assessment of iron deficit [71]. In the very elderly, it is difficult to establish a diagnosis because the disease is not only uncommon but the presenting symptoms are mild or atypical [20] as in this patient. A single case of Crohn's disease in a 92-year-old male had been reported [72] who presented with abdominal pain, and initial diagnosis was ischaemic colitis. In the older patient, distal ileum is the commonest site and the presentation is acute after initially mild symptoms [21]. A number of medications are available such as corticosteroids (oral and topical), 5-aminosalicylates, immunomodulators, antibiotics and biological agents. An 8-week trial on budesonide was found to have been effective for active Crohn's disease of the ileum and proximal colon [73].

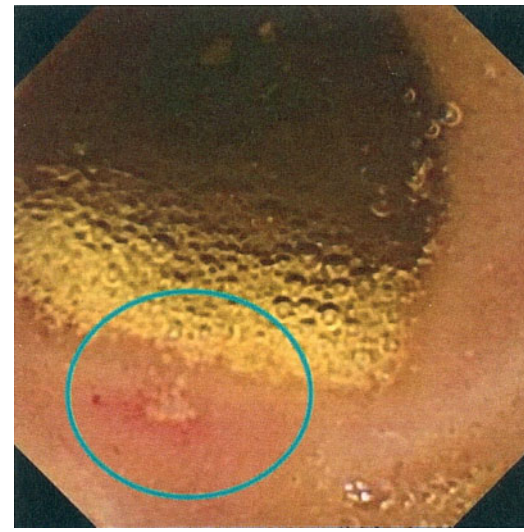

Fig. 1 Shows an aphthous ulcer

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Gastrointestinal Bleeding in the Elderly

18

Contents

Abstract

Gastrointestinal bleeding is any bleeding into the lumen of the gastrointestinal tract from the oesophagus to the anus. The ageing process together with the co-morbidities and the greater use of medications such as NSAIDs and anticoagulants have a negative effect on the outcome of GI bleeding in the elderly. In the elderly because of the alterations in pain perception and atypical presentation, certain gastrointestinal disorders can present with difficulty in diagnosis. The present review will highlight the causes and discuss the management of gastrointestinal bleeding in the elderly.

Keywords

Gastrointestinal bleeding · Upper gastrointestinal bleeding · Lower gastrointestinal bleeding · Mallory-Weiss syndrome · Angiodysplasia

Introduction

Gastrointestinal bleeding is any bleeding into the lumen of the gastrointestinal tract from the oesophagus to the anus. It can range from being undetectable to acute massive and life threatening. Gastrointestinal (GI) bleeding is common among the older men and women. Each year more than 1% of the people aged 80 years or more are hospitalised because of gastrointestinal bleeding [1]. In the United States, it ranges from 20.5 to 27 per 100,000 persons per year and is more common in men than in women [2]. Bleeding can occur either from the upper or lower gastrointestinal tract. The incidence of upper GI bleeding (UGIB) is between 47 and 116 per 100,000 population [3] and is about four times as common as lower gastrointestinal bleeding (LGIB) [4]. GI bleeding increases with age; in lower GI bleeding, there is greater than 200-fold increase from the third to the ninth decades of life [5].

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_19

GI bleeding is associated with higher rates of hospitalisation [6], increased morbidity and mortality in the elderly than in the young and is a common medical emergency [7, 8]. The ageing process together with the co-morbidities and the greater use of medications such as NSAIDs and anticoagulants have a negative effect on the outcome of GI bleeding in the elderly [9]. In the elderly because of the alterations in pain perception and atypical presentation, certain gastrointestinal disorders can present with difficulty in diagnosis [9].

Upper Gastrointestinal Bleeding (UGIB)

In the elderly upper gastrointestinal bleeding (UGIB) is common and notably a life-threatening condition [7]. Most deaths occurring in the elderly are due to co-morbidities such as liver disease, renal failure and diabetes. Age is an independent risk factor for mortality and widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs), *H. pylori* infection [7] and in part diminished compensatory reserve are causal risk factors. The bleeding whether brisk or protracted is due to one of the following conditions (see Box 1): peptic ulcer, oesophageal or gastric malignancies, oesophageal varices, Mallory-Weiss tear, erosive lesions and oesophagitis, and they account for 90% of the patients with a diagnosis with upper gastrointestinal bleeding [10, 11].

Box 1 Causes of Upper Gastrointestinal Bleeding

	Percentage
Peptic ulcer	20
Varices	5
Esophagitis	10
Mallory-Weiss	5
Erosive disease	6
Neoplasm	4
Vascular malformations	5
Rare or other	6
No obvious cause	24

Information source: Dallal and Palmer [4]

The mechanisms of peptic ulcer formation are unclear. The processes probably involve an interplay of *Helicobacter pylori* infection, acid secretion, pepsin secretion and mucosal defence mechanisms. Other risk factors include alcohol abuse, smoking, chronic renal failure, NSAIDs, age and lower socio-economic class among others and may either cause or aggravate the disease [12]. Peptic ulcer disease causes significant morbidity and mortality in the elderly [13]. The prevalence of *Helicobacter pylori* infection increases with age [13], and more than 90% of the patients over the age of 65 years with peptic ulcer disease are infected with *H. pylori*. It attaches to the epithelium and causes apoptosis and triggers an inflammatory response.

The higher incidence of ulcer complications in the elderly is indicative of a higher prevalence of *H. pylori* infection with an interaction between *H. pylori* infection and use of NSAID [14]. *H. pylori* infection is associated with a low risk of gastric bleeding [14]. A *H. pylori*-positive NSAID user has a lower risk than *H. pylori*-negative NSAID user [14]. *H. pylori* is also associated with antral gastritis and is a significant risk factor for gastric carcinoma.

Oesophagitis is a mucosal damage caused by gastro-oesophageal reflux, and bleeding can occur and can be life threatening. Mallory-Weiss syndrome (laceration of the distal oesophagus and proximal stomach) is the cause of UGIB in about 5% of patients [4] and follows retching and vomiting. In most instances, the bleeding ceases spontaneously and occasionally may require ligation of the laceration.

Vascular malformations and angiodysplasia are well-described causes of upper and lower gastrointestinal tract bleeding and present with massive haematochezia. Identifying them when not actively bleeding can be difficult they are often small and multiple [15, 16]. CT angiography and angiography are useful and have a sensitivity from 56% to 86% [17].

Oesophageal varices and less commonly gastric varices secondary to portal hypertension and cirrhosis of the liver are prone to bleeding which is often massive.

Oesophageal carcinoma is one of the most common cancers in the world and occasionally could present with gastrointestinal bleeding as the main symptom.

Malignant neoplasms of the stomach include adenocarcinoma (90%) and are the most common cancer worldwide [18]; lymphoma (5%) and others such as leiomyosarcoma, squamous cell carcinoma and carcinoid may present with haematemesis or melaena. Characteristics of upper gastrointestinal bleeding (UGIB) are summarised in Table 1.

Lower Gastrointestinal Bleeding (LGIB)

The mean age of people with LGIB ranges from 63 to 77 years [9]. About 80% of the diseases develop in the rectum and sigmoid colon. LGIB can present as an acute, occult or obscure bleeding. In the acute, haematochezia (red blood per rectum) and in some instances melaena together with symptoms of abdominal pain, lightheadedness and rectal urgency occur. With significant blood loss, there may be orthostatic hypotension. LGIB stops spontaneously with supportive therapy [8], and the reported mortality rate ranges from 2% to 4% [9].

The common causes of LGIB in the elderly are diverticulosis coli, vascular ectasia, polyps haemorrhoids [8] ischaemic colitis and colonic neoplasms [5].The most common cause of LGIB in the elderly people is diverticular haemorrhage, and this is due to the increase in incidence of diverticular disease in this group [19]. Diverticulosis is a disease of advancing age in Western countries and is often considered as part of normal ageing. In the Western world, more than half the population above the age of 70 years develop diverticulosis [20]. The prevalence is estimated at approximately 5%, and this increases to 65% in the 65 years and over and 80–85% remain asymptomatic. Diverticulitis affects 10–25% of patients with diverticulosis [21]. It has been suggested that dietary changes [22] have influenced the prevalence of diverticulosis, and this is consistent with the geographic distribution. Consumption of refined carbohydrate and lack of adequate fibre [23–25] contribute to its occurrence. Vegetarians have a low prevalence.

Table 1 Characteristics of upper gastrointestinal bleeding

Disease/ incidence	Nature of bleeding	Associated symptoms	Associated signs	Complications	Investigations
Peptic ulcer 20%	Haematemesis/ melaena	Epigastric pain/vomiting anorexia	Hypotension in acute haemorrhage	Perforation	Fibroendoscopy
				Obstruction to outflow	*H. pylori*, serum gastrin
Oesophageal varicies 5%	Haematemesis/ melaena	Cirrhosis	Massive		
		Portal hypertension			
Vascular/ angiodysplasia 5%	Haematochezia	Painless			Acute phase
					Angiography
	Recurrent				Pill camera
Neoplasia 4%	Haematemesis/ melaena	Epigastric	Mass, pallor	Obstruction	Fiberoptic endoscopy
		Pain/early satiety	Node in supraclavicular fossa		Double-contrast barium meal
					CT
Mallory-Weiss 5%	Haematemesis	Retching, vomiting	Usually self-limiting		
Oesophagitis 10%	Melaena/ haematochezia	Heart burn regurgitation		Can be life-threatening aspiration stricture, Barret's, pneumonia	Endoscopy
					Radiography

Information sources: Dallal and Palmer [4], Rockall et al. [10] and Blatchford et al. [11]

Diverticulosis occurs in any part of the large bowel but more especially in the sigmoid colon. About 75% of the patients are asymptomatic, and 10–20% deny clinical symptoms [21]. Bleeding from diverticulosis is often brisk and profuse with the passage of bright red blood or dark red blood from the rectum. It is nearly always painless, only with mild abdominal cramping. Occasionally the bleeding may be massive and is caused by erosion of the adjacent vessel and secondary to impacted faeces, and the patient is seen in haemorrhagic shock. In most instances however, the bleeding is self-limiting [26]. Although majority stop bleeding spontaneously, angiographic and surgical treatment may be required [26]. The patients with diverticulosis do not experience occult gastrointestinal blood loss as the bleeding results from rupture of a vessel. If occult blood is found in the presence of diverticulosis, it will be necessary to consider another possible cause, for instance, carcinoma. Diagnosis is by CT scan and colonoscopy [26, 27]. - Perivascular abscesses, perforation, fistulas, strictures and or obstruction are the complications of diverticulitis [28].

Angiodysplasia is known to cause LIGB as frequently as diverticulosis. Angiodysplasia is one of the commonest causes of LGIB in the elderly [17] and accounts for 6% of LGIB [29]. It may present with melaena, haematochezia, occult blood or iron deficiency anaemia [30]. The bleeding tends to be recurrent in contrast to diverticular bleeding which is brisk and usually not recurrent. In most instances, the bleeding ceases spontaneously. Colonic ectasia is an increasingly recognised cause of gastrointestinal haemorrhage [31].

The term colitis applies to inflammatory diseases of the colon such as ulcerative colitis, Crohn's disease, ischaemic colitis, infectious colitis and radiation colitis. In a study of 81 patients with colitis over the age of 65 years, 75% were suffering from ischaemic colitis, 14% ulcerative and 5% Crohn's disease [32]. Ulcerative colitis has a bimodal distribution with a high peak at 30 and 40 years and a second smaller peak at ages 50–70 years. This secondary rise is said to be due to ischaemia [33] and includes cases of ischaemic colitis. In ulcerative colitis, there is bloody diarrhoea of varied intensity and with asymptomatic intervals. There are blood and mucous in the stools with an urgency to defaecate and lower abdominal cramps.

Ischaemic colitis primarily occurs in the elderly due to non-occlusive mesenteric ischaemia and is characterised by significant co-morbidities [34]. Transient episodes of colonic hypoperfusion, often precipitated by dehydration, result in ischaemic colitis. The patients with ischaemic colitis present with cramping abdominal pain and CT scan shows thickening of the colon. In elderly patients when the disease affects the right colon, it may produce negative outcome [34]. In haemorrhoids bleeding is painless, and typically the blood is on the surface of stool and occult blood should not be attributed to haemorrhoids (Table 2).

Evaluation of a Patient with Gastrointestinal Bleeding

A careful history and a complete physical examination may guide investigations as to the source of the bleeding [35] together with an understanding of the gastrointestinal lesions likely to cause bleeding in the elderly which could serve to distinguish whether the bleeding is from the upper or lower gastrointestinal tract. In many instances, the clinical signs may contribute to location as well as the possible cause of the disorder. Haematemesis, tarry stool (melaena) or the presence of blood in the patient's nasogastric lavage are suggestive of UGIB, whereas bright red blood per rectum (haematochezia) is from the lower gastrointestinal tract. The presence of chronic stigmata of chronic liver disease, ascites and jaundice is suggestive of liver disease. Gastrointestinal bleeding can be classified as (i) acute which may be life threatening [36]; presenting with haematemesis, melaena or haematochezia; or (ii) chronic suspected because of the presence of anaemia or occult blood [36].

It is highly relevant to identify patients with low probability of re-bleeding from those with a high probability [37]. Various methods have been

Table 2 Characteristics of lower gastrointestinal bleeding

Disease/incidence	Nature of bleeding	Associated symptoms	Associated signs	Complications	Investigations
Diverticular disease 5–65%	Haematochezia dark/bright red (arterial)	Almost painless self-limiting	Occasionally massive	Shock	
Vascular/ angiodysplasia 6%	Haematochezia venous	Recurrent May stop spontaneously			In acute-phase angiography
Haemorrhoidal	Blood typically on surface of stool	Painless	Recurrent	Thrombosis/ strangulation	Anoscopy/ sigmoidoscopy
Neoplasm	Acute haemorrhage occasionally occult blood	Change of bowel habits, tenesmus		Obstruction Perforation	Colonoscopy FOBT
Ischaemic colitis		Cramping abdominal pain			
Inflammatory colitis	Blood and mucous	Varied intensity urgency/lower abdominal pain	Interspersed with asymptomatic intervals	Perforation haemorrhage strictures	Colonoscopy Barium enema Stools culture

Information sources: Maier [21], Foutch [29], and Barnert and Messman [36]

devised to assess risk of re-bleeding. The Rockall scoring system was designed to predict the risk of re-bleeding and death after admission to hospital for acute UGIB. A series of independent risk factors including age, the presence of shock, co-morbidity, diagnosis and recent haemorrhage on endoscopy were scored, and the total score predicts outcome. A score of 2 or less has a mortality of 0.14 and a re-bleeding rate of 4.3%, whereas a score in excess of 8 is associated with 41% mortality and re-bleeding of 42.1% [38]. Persistent or recurrent bleeding occurs in 5–30% [39]. Evaluation would be foremost to determine the acuity and pace of the blood loss and focus on haemodynamic stabilisation and followed by diagnostic evaluation to determine the bleeding source.

In both acute and chronic bleeding, colonoscopy is the procedure of choice [36]. It is recommended in the early evaluation of LGIB [40]. The diagnostic yield of colonoscopy ranges from 48% to 90% [41]. In many centres with negative or failed colonoscopy, computerised tomography (CT) has become the next procedure in the acute setting [35]. Catheter angiography and red cell labelling techniques have limited sensitivity and specificity [35].

Occult bleeding is the most common form of gastrointestinal bleeding [42] and detected when faecal occult blood tests are positive or in the presence of iron deficiency anaemia [42–44]. Iron deficiency anaemia should be considered as due to GI bleeding till proved otherwise [42]. Initial step in the evaluation of occult blood would be oesophagogastroduodenoscopy and colonoscopy [43, 44], and if negative a repeat may find missed lesions [43]). If a cause has not been found, the next step is capsule endoscopy [42, 44] which has a diagnostic yield of 61–78% [43]. In patients with active bleeding, radionuclide red call scans or angiography may be useful [44]. Treatment often involves endoscopic ablation of the bleeding site or angiographic embolisation [26] for lesions that cannot be reached endoscopically [44].

Impact

Upper gastrointestinal bleeding is a potentially life-threatening condition among the elderly. Patients admitted with UGIB have a mortality of about 11% [45] and is as high as 33% in patients who develop bleeding while in hospital. After the

initial bleed, the risk factors for re-bleeding are associated with higher mortality, and several factors such as older age, co-morbidity, intestinal ischaemia and haemodynamic instability may contribute [36]. The mortality rate is 4–10% or higher in patients hospitalised for acute lower gastrointestinal bleeding in the age group from third to ninth decades [46] (Box 2).

Box 2 Key Points. Gastrointestinal Bleeding in the Elderly

Each year more than 1% of the people aged 80 years or more are hospitalised because of gastrointestinal bleeding [1].

GI bleeding is associated with higher rates of hospitalisation [6], increased morbidity and mortality in the elderly than in the young and is a common medical emergency [7, 8].

The ageing process together with the co-morbidities and the greater use of medications such as NSAIDs and anticoagulants have a negative effect on the outcome of GI bleeding in the elderly [9].

Upper gastrointestinal bleeding (UGIB) is four times as common as lower gastrointestinal bleeding (LGIB) [4].

Peptic ulcer, oesophageal or gastric malignancies, oesophageal varices, Mallory-Weir tear, erosive lesions and oesophagitis account for 90% of the patients with a diagnosis with upper gastrointestinal bleeding [10, 11].

In the elderly the alterations in pain perception and atypical presentation diagnosis can be difficult [9].

Most of the deaths are due to co-morbidities such as liver disease, renal failure and diabetes.

The most common cause of LGIB in the elderly is diverticular haemorrhage. Angiodysplasia is known to cause LIGB as frequently as diverticulosis.

Ischaemic colitis primarily occurs in the elderly due to non-occlusive mesenteric ischaemia.

Box 2 Key Points. Gastrointestinal Bleeding in the Elderly (continued)

It is highly relevant to identify patients with low probability of re-bleeding from those with a high probability [37].

Evaluation would be foremost to determine the acuity and pace of the blood loss and focus on haemodynamic stabilisation, followed by diagnostic evaluation to determine the bleeding source.

Multiple Choice Questions

1. The following are true in relation to gastrointestinal bleeding, *except*:
   A. Upper gastrointestinal bleeding is four times as common as lower gastrointestinal bleeding.
   B. Ninety percent of peptic ulcer disease and 99% of duodenal ulcer are associated with infection by *H. pylori.*
   C. *H. pylori* is associated with antral gastritis and is a significant risk factor for gastric carcinoma.
   D. Diverticular haemorrhage in the elderly is far from common.
2. The following statements relating to diverticular haemorrhage are true, ***except***:
   A. The bleeding with diverticulosis is due to rupture of a vessel.
   B. The diverticular bleeding is brisk and recurrent.
   C. If occult blood is present in a patient with diverticular disease, it will be necessary to consider another diagnosis.
   D. The most common cause of lower intestinal bleeding in the elderly is diverticular haemorrhage.
3. The following in relation to gastrointestinal bleeding are true, *except*:
   A. Blood on the surface of the stool and occult blood could be attributed to haemorrhoids.
   B. Chronic bleed is suspected because of the presence of occult blood or anaemia.
   C. Signs of shock, pulsatile haemorrhage, coagulopathies and cardiovascular diseases are risk factors for re-bleeding.

D. Ischaemic colitis in the elderly is due to non-occlusive mesenteric ischaemia.

MCQ Answers

1=D; 2=B; 3=A

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Acute Abdominal Pain in the Elderly

19

Contents

Abstract

Abdominal pain can be due to many causes, and the underlying pathology could be due to an infection, mechanical obstruction, biliary disease, malignancy and gastrointestinal ischaemia. The prevalence of acute abdominal pain increases with advancing age. Among the elderly presenting to the emergency department, approximately 50% were hospitalized and 30–40% eventually had surgery. This review provides an overview of acute abdominal pain in the elderly, prevalence, causes and management.

Keywords

Acute abdominal pain · Infection · Mechanical obstruction · Biliary disease · Malignancy · Gastrointestinal ischaemia

Introduction

Acute abdominal pain can be defined as pain lasting for less than 1 week in duration [1]. About 25% of the patients seen in the emergency department with acute abdominal pain are over the age of 50 years [2, 3]. Among the elderly presenting to the emergency department, approximately 50% were hospitalized and 30–40% eventually had surgery [4, 5], and 40% were misdiagnosed contributing to an overall mortality of approximately 10% [6], and from other retrospective studies the mortality varies from 2% to 13% [7–9]. There is no doubt that acute abdomen in the elderly is of great importance both of the frequency of occurrence and the high mortality.

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_18

The prevalence of acute abdominal pain increases with advancing age. The number of old people is expected to increase in the future; as acute abdominal pain increases with age, there will be more elderly seen requiring correct diagnosis, investigation and immediate and appropriate treatment. Acute abdomen has a threshold of clinical significance in the elderly just as much as in the other age groups.

Abdominal pain can be due to many causes, and the underlying pathology could be due to an infection, mechanical obstruction, biliary disease, malignancy and gastrointestinal ischaemia [10]. The pathology of acute abdomen in the elderly are the same as in younger age groups however the relative prevalence of each may be different (Box 1).

Causes

Box 1 Causes of Abdominal Pain
Appendicitis
Biliary tract disease
Peptic ulcer disease
Diverticulitis
Bowel obstruction
Mesenteric ischaemia
Abdominal aortic aneurysm
Malignancy
Pancreatitis
Gastroenteritis
Nonsurgical causes

Appendicitis

Acute appendicitis occurs increasingly with advancing age and accounts for significant morbidity and mortality. The mortality rate is 16 times higher than in the younger individuals [11]. The diagnosis and treatment are often delayed. Some of the contributing factors to this are the presence of concomitant illnesses and the multiplicity of differential diagnostic possibilities in this age group [12]. Only about 20% of the elderly presented with classic appendicitis [13]. The elderly with acute appendicitis may have generalized pain that is not followed by localization to the right lower quadrant. They are likely to present with long duration of pain, distension, rigidity, decreased bowel sounds and a palpable mass [1]. In one study of 96 elderly patients over the age of 60 years with appendicitis only 20% had the classic combination of fever, nausea, pain in right lower quadrant and an elevated white cell count [14]. In the same study only 23% had either diffuse abdominal tenderness or tenderness in the right lower quadrant and fever in 47%. About half the patients over the age of 60 years were seen 72 h after the onset of symptoms with abdominal pain and tenderness but had relatively minimal associated symptoms and findings [12]. A multicentre study however found the intensity of pain was more severe (61% vs 46%) and more frequent association with change in bowel habits (8% vs 2%) in the elderly [15]. Perforation occurred in 37% of the elderly with acute appendicitis compared to 4% in younger patients [13]. In about 91% of the patients with misdiagnosis had ruptured appendix [16]. Contrast-enhanced spiral computed tomography aided diagnosis [17, 18]. Neither the CT nor a laproscopy appendicectomy has affected the outcome, but overall results might improve with early diagnosis in the elderly patients with abdominal pain and prompt surgical consideration and treatment [19].

Cholecystitis

Cholecystitis, gall stones and carcinoma of the gall bladder account for more than one-third of the abdominal operations one in the 75 years and over elderly. In a study of 88 patients over the age of 60 years with biliary tract disease, the mortality was 6.8% [20]. The patient with acute cholecystitis usually presents with unremitting and increasing pain in the right upper quadrant and often associated with fever and vomiting. A significant percentage of older patients do not have the classic symptoms of cholecystitis. About 25% of elderly patients do not have significant pain, and less than half have fever or elevated white cell count [13].

Complications of acute cholecystitis occur in more than half of all patients over the age of 65 years, and such complications include acute ascending cholangitis, gallbladder perforation, bile peritonitis, emphysematous cholecystitis and gallstone ileus [1]. Forty percent of 88 elderly patients with acute cholecystitis, 21% had empyema of the gall bladder, 18% gangrenous cholecystitis or free perforation of the gall bladder and 15% had subphrenic liver abscess [20]. About 10% with cholecystitis will die [13].

Acute cholangitis is usually due to impacted stone in the ampulla of Vater or secondary to cancer of the pancreas. The elderly have a high incidence of acute cholangitis [21]. The clinical presentation is wide spectrum from a mild to severe or suppurative cholangitis [22] and has a significant mortality in the elderly [23, 24]. Active treatment of acute cholangitis in the elderly may decrease the need for emergency surgery. Malnutrition and perforation of the gall bladder were found to be the most important predictors of mortality in this patient group [25].

Peptic Ulcer Disease

Peptic ulcer disease causes significant mortality and morbidity in the elderly. NSAIDs inhibiting prostaglandin synthesis and *H. pylori* infection (in 70% of patients) are the most important causal factors and contribute to the high incidence of ulcers. There are several possible explanations for the increased risk in elderly patients. Inevitably in the elderly there will be an increased incidence of comorbidities such as degenerate cardiac and respiratory diseases. In one study of patients over the age of 60 years with duodenal and gastric ulcers 72% had at least one other medical condition, 20% two or more [26]. Peptic ulcer disease frequently presents in an atypical manner and is associated with a high incidence of complications. Symptoms can be vague, and the first sign of the disease is with a complication such as perforation [1] or gastrointestinal bleeding [27]. The NSAIDs can mask the pain in the elderly, and gastrointestinal bleeding can be painless. Bleeding is the most important complication occurring in 50%, perforation in 2% [28].

Diverticulitis

About 50% of the elderly over the age of 60 years have colonic diverticulosis, and 10–25% develop complications such as diverticulitis [29]. Pain of diverticular disease is different to that of diverticulitis, mild forms present with gradually increasing symptoms, whereas acute complicated disease is associated with sudden onset of pain followed by fever [30]. Painful diverticular disease is characterized by colicky abdominal pain and often provoked by eating, passing wind or bowel movement. There may be tenderness in the left lower quadrant. Diverticulitis is characterized by abrupt onset, unremitting left lower quadrant pain with fever, chills, nausea and vomiting. Diarrhoea or constipation can occur in an alternating bowel pattern. Diverticulitis of the caecum or redundant sigmoid colon may simulate appendicitis and involving the transverse colon, peptic ulcer. Diverticulitis may result in perforation of the colonic diverticulum [30]. Plain x-rays are helpful, and CT scan is the test of choice to evaluate acute diverticulitis. Ultrasound is an alternative to CT.

Abdominal Aortic Aneurysm (AAA)

Patients who are at risk are those with a family history, hypertension, peripheral arterial disease and smoking. More than 90% of AAA are below the renal arteries extending to either or both iliac arteries. Significant AAAs may be symptomatic or the patient may present with deep, boring pain felt in the low back and an prominent pulsatile abdomen which the patient may not be aware. The risk of rupture is dependent on the size, the presence of hypertension, chronic obstructive airway disease and occlusive arterial disease [31]. Signs and symptoms of a ruptured AAA are excruciating abdominal pain, in the back [32] or flank, and depending on the severity hypovolaemic hypotension and a pulsatile mass or shock [32]. A pulsatile

mass with flank ecchymosis is highly suggestive of a ruptured AAA [1]. The differential diagnosis includes the above-mentioned conditions.

Ultrasound is non-invasive and gives a clear picture of the extent and size of the aneurysm. Indications for referral are, in the male >5.5 cm, female >5.0 cm, rapid growth of more than 1.0 cm/year and symptoms such as abdominal pain, tenderness and distal embolization [33]. With the introduction of the aortic stent, there has been a significant change in the mortality and morbidity in the elderly patient [34]. The treatment of AAA in the elderly CT is done for clinically stable patients to identify dissecting or leaking aneurysm. In a study of AAA in patients over the age of 70 years, all those with expanding or ruptured aneurysms had abdominal pain or back pain and most of those with ruptured aneurysm were in shock. The mortality rates for the elective, expanding and ruptured groups were 4.5%, 12.5% and 60.8%, respectively, and the common cause of death in the ruptured group was multisystem failure [32]. The risk of operative treatment of AAA after rupture is high compared to elective, and about 65% die at home with rupture or during transport to hospital [35]. The mortality of open repair for ruptured aneurysm is 30–40% [33].

Acute Mesenteric Ischaemia

Intestinal ischaemia has been classified as acute mesenteric ischemia (AMI), chronic mesenteric ischaemia (intestinal angina) and colonic ischaemia [36]. Acute mesenteric ischaemia is uncommon and constitutes 1% of admissions for acute abdominal pain [37], and the mean age is 71 years (range 25–100 years) [38]. The overall mortality is between 50% [38] and can rise to 80% if infarction is present [39] and in case of missed diagnosis, it is 90% [39]. The ischaemia can be the result from occlusion or non-occlusive hypoperfusion and frequently results in bowel necrosis and death [39]. Acute occlusion results from embolism, acute thrombosis or aortic dissection. Atherosclerosis or fibromuscular hyperplasia usually gives rise to chronic occlusion.

With acute occlusion, the patient presents with severe abdominal pain often accompanied by vomiting and an urge to defaecate. The abdomen may be tender but the abdominal pain is disproportionate to the abdominal findings. Some patients with AMI may initially complain of vague abdominal discomfort in the lower abdomen with nausea, vomiting and diarrhoea [37]. The late findings include abdominal distension, shock peritoneal irritation and signalling infarction [40]. The clinical diagnosis is often uncertain until laparotomy, but sudden onset of abdominal pain and bloody stool in the elderly are very suggestive of this condition. There may scattered loops of dilated bowel with multiple fluid levels or fluid-filled loops of small bowel on plain x-rays. The walls of the small intestine may be thickened and oedematous in less than 40% [40]. CT angiography is the diagnostic gold standard for AMI, and magnetic resonance angiography has comparable exactness [40], and both have emerged as alternatives and less invasive [41]. High index of suspicion together with early diagnosis can improve the outcome [31] The initial management includes rapid haemodynamic monitoring [41] which includes vigorous hydration, resuscitation and treatment of the underline aetiology [40].

Bowel Obstruction

Large bowel obstruction – Colonic obstruction includes tumours, diverticular disease, volvulus and rarely by compression from a pelvic tumour. Carcinoma of the colon is the most commonest cause and does not cause pain unless there is obstruction. Sigmoid volvulus is the most common type of colonic volvulus [42]. Symptoms are usually insidious with colicky abdominal pain, nausea and vomiting. In the elderly patients with intestinal obstruction, the mortality due to surgery is related to perianaesthetic risk and delay in surgery [43].

Small bowel obstruction – Majority of the patients with mechanical obstruction of the small bowel will have adhesions due to previous surgery or obstruction due to strangulated hernia. Obstruction due to adhesive bands may occur in combination with volvulus of the small intestine as an

isolated lesion. Symptoms are somewhat similar to large bowel obstruction. The use of water-soluble contrast (gastrografin) has strong support as a predictive test for nonoperative resolution of adhesive small bowel obstruction [44, 45]. In the elderly delay in surgery in patients with complete small bowel obstruction leads to increase in complications and length of hospitalization [46].

Acute Pancreatitis

The incidence of acute pancreatitis in the United Kingdom is rising and ranges from 150 to 420 cases per million population [47]. About 50% of the cases with acute pancreatitis are associated with gall bladder disease, and 20–25% is related to alcohol abuse [47]. Patient with acute pancreatitis usually present with pain in the epigastrium or peri-umbilical region and radiating to the back which is worse on lying down but relieved by standing. There is intractable vomiting. The abdomen is tender, distended and decreased bowel sounds. Serum amylase is elevated and may remain elevated for some time and is used as a diagnostic indicator, but its half-life is shorter than that of lipase [47]. Hence serum lipase persists longer after the acute attack and has a slightly greater sensitivity and specificity [47]. Persistent elevation of the enzymes in an asymptomatic patient may suggest the presence of a pseudocyst. The diagnosis of acute pancreatitis is usually made clinically but may be difficult in a critically ill or postoperative patients or patients with major abdominal trauma. Advanced age is an indicator of poor prognosis. And the mortality rate in older patients is about 20–25% [48].

Clinical Considerations

Acute abdominal pain in the elderly is one of the commonest and most important problems confronting the physician and surgeon alike. The elderly with acute abdominal pain have a higher degree of morbidity and mortality and is largely due to the delay in diagnosis, delay in treatment and the presence of co-morbidities. There are a variety of reasons for the delay in diagnosis. About 10% of the elderly presenting with acute abdominal pain to the emergency have atypical symptoms which delay diagnosis [49]. The elderly tend to delay in seeking medical care. The delay in seeking medical care to psychosocial factors such as fear of hospitalization, fear institutionalization and loss of independence makes light of the symptoms, and many old people may think abdominal pain is part of normal aging process and are less likely to complain.

Many old people have some degree of cognitive decline and may not be able to provide a proper history. Traditionally the cornerstone of diagnosis is a thorough history and physical examination, and these may be difficult or impossible in the elderly patient more so when the memory is impaired. The perception of pain and pain intensity in those cognitively intact or cognitively impaired has been claimed to be of no difference [50]. Blunt pain perception may be due to common age-associated diseases such as diabetic neuropathy or the chronic use of medications, and diminished sensation may allow the pathology to progress to an alarming point.

The presentation of an elderly with abdominal pain may be atypical from that seen in the younger patient [51–53]. Fever and leucocytosis associated with acute abdomen may evoke a decreased response in older people [54]. Pain is usually a feature, and a pain-free acute abdomen is more likely in the elderly. A large number of medical conditions can simulate acute abdominal pain (Box 2).

Box 2 Nonsurgical Disease

Pneumonia
Myocardial infarction
Pericarditis
Hepatitis
Inflammatory bowel disease
Acute intermittent porphyria
Opiate withdrawal
Typhoid
Sickle cell crisis
HIV-associated lymphadenopathy

Evaluation of a Patient with Acute Abdominal Pain

A careful history and a thorough physical examination as well as a high index of suspicion are central to avert a missed diagnosis. The pressing need is to recognize likely life-threatening acute abdominal conditions that require resuscitation, immediate investigation and early surgical assessment and intervention [55]. The differential diagnosis is extraordinarily broad and may include the potentiality for referred pain. In the elderly myocardial infarction, pulmonary embolism, acute heart failure, pneumonia, urinary tract infarction and constipation among others may present as acute abdominal pain. A definite diagnosis is often difficult especially in primary care.

There are differences in the presentation of acute abdominal pain in the elderly compared to the young. The patient is rapidly inspected for evidence of shock, haemorrhage, dehydration, anaemia or cardiac decompensation. The abdominal examination should include a rectal examination in the male and rectal and pelvic in the female and the hernial orifices and bowel sounds checked. Palpation both light and deep for area of maximal tenderness. Rebound tenderness indicative of peritonitis may not be reliable in the elderly for in large number of the elderly it is may be absent. More reliable would be the finding of involuntary guarding of the area of greatest pain. Point tenderness is the most important sign of peritonitis. In a study of 127 elderly patients in the emergency department with acute abdominal pain, 24% [35] had no specific diagnosis, and 12% had biliary tract disease, and of 125 patients with small bowel obstruction, 42% required surgery and in 14 patients the follow-up diagnosis was different from the original diagnosis [56].

Blood chemistry can be misleading. The white blood cell count may be normal in the elderly. The liver panels and arterial blood gases can be useful. More than half of the patients with acute pancreatitis have elevated serum amylase. The use of abdominal imaging studies assists in effective assessment [10]. Plain x-ray of the abdomen in the supine and upright positions may show fluid levels, free air in the peritoneum cavity and distended bowel for mesenteric ischaemia and obstruction. In a study comparing imaging strategies, CT had the largest increased in diagnostic accuracy after clinical evaluation and following a conditional strategy with CT after a negative or inconclusive ultrasonography resulted in the highest overall sensitivity [55]. The investigators recommended that ultrasonography as the initial investigation on patients with acute abdominal pain [55]. The new generation of spiral CT scanner gives excellent views of vascular and digestive pathologies [56].

Impact

Among the elderly presenting to the emergency department, approximately 50% were hospitalized, and 30–40% eventually had surgery [4, 5], and 40% were misdiagnosed contributing to an overall mortality of approximately 10% [6]. The diagnosis and treatment, for example, of appendicitis are often delayed. Some of the contributing factors to this are the presence of concomitant illnesses and the multiplicity of differential diagnostic possibilities in this age group [12]. In the elderly there is a high incidence of complications, and several factors contribute to the diagnostic difficulty [57]. Waning of immune function with advancing age, together with the presence of co-morbidities such as malignancy or diabetes, further suppresses immunity [57] (Box 3).

Box 3 Key Points. Acute Abdominal Pain in the Elderly

Among the elderly presenting to the emergency department, approximately 50% were hospitalized and 30–40% eventually had surgery [4, 5], and 40% were misdiagnosed contributing to an overall mortality of approximately 10% [6].

Abdominal pain can be due to many causes, and the underlying pathology could be due to an infection, mechanical obstruction, biliary disease, malignancy and gastrointestinal ischaemia.

(*continued*)

Box 3 Key Points. Acute Abdominal Pain in the Elderly (continued)

Acute appendicitis occurs increasingly with advancing age, and the mortality rate is 16 times higher than in the younger individuals [11].

The diagnosis and treatment are often delayed. Only about 20% of the elderly present with classic appendicitis [13].

About 25% of elderly patients with cholecystitis do not have significant pain, and less than half have fever or elevated white cell count [13].

Symptoms of peptic ulcer disease can be vague, and the first sign of the disease is with a complication such as perforation [1] or gastrointestinal bleeding [27].

Advanced age is an indicator of poor prognosis, and the mortality rate in older patients with acute pancreatitis is about 20–25% [38].

In the elderly myocardial infarction, pulmonary embolism, acute heart failure, pneumonia, urinary tract infection and constipation, among others, may present as acute abdominal pain.

Multiple Choice Questions

1. The following in relation to acute abdominal pain in the elderly are true *EXCEPT:*
   A. Fever, pain, guarding, rigidity and leucocytosis may evoke an increased response in the elderly with acute abdominal pain.
   B. Elderly tend to seek medical care late.
   C. The presentation of acute abdomen may be atypical in the elderly.
   D. Pain is usually a feature but a pain-free abdomen is more likely in the elderly.
2. The following statements are true in relation to acute abdominal pain *EXCEPT:*
   A. The elderly with acute appendicitis have generalized pain that is not followed by localization in the right lower quadrant.
   B. Contrast-enhanced spiral computed tomography aids diagnosis in acute appendicitis.
   C. A significant percentage of older patients do have classic symptoms of acute cholecystitis.
   D. In the age group 65 years and over, complications of acute cholecystitis occur in more than half the patients.
3. The following are true in relation to acute abdominal pain *EXCEPT:*
   A. NSAIDs inhibiting prostaglandin synthesis and *H. pylori* are the most important causal factors that contribute to the high incidence of peptic ulcers.
   B. In the elderly with peptic ulcer, symptoms can be vague, and the first sign of the disease is a complication like perforation.
   C. CT is not the best to evaluate acute diverticulitis
   D. In diverticulitis diarrhoea or constipation can occur as alternating bowel pattern.
4. The following are true *EXCEPT:*
   A. More than 90% of abdominal aortic aneurysm (AAA) is above the renal arteries.
   B. Ultrasonography is non-invasive and gives a clear picture of the extent and size of the abdominal aortic aneurysm.
   C. In acute pancreatitis serum amylase is elevated only for a short time.
   D. In acute mesenteric ischaemia, there may be scattered loops of dilated bowel with multiple fluid levels or fluid-filled loops of small bowel on plain x-rays.

MCQ Answers

1 = A; 2 = C; 3 = C; 4 = A

Short Answer Questions

1. List four conditions that can mimic acute abdominal pain.

SAQ Answers

1. pneumonia
2. myocardial infarction
3. pericarditis
4. hepatitis

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Infectious Diarrhoeas in the Elderly

20

Contents

Abstract

Diarrhoea can be mild or severe in the elderly and severe diarrhoea in the elderly can be life-threatening. *Clostridium difficile* is the most common cause of nosocomial diarrhoea and disproportionally affects the elderly and in those above the age of 65 years and remains a disease of the elderly. The elderly are at increased risk of dying from dehydration and electrolyte abnormalities and impaired mobility and are frequently institutionalised. The present review summarises the infectious diarrhoeas with the main focus on *Clostridium difficile* and management.

Keywords

Diarrhoeas in the elderly · *Clostridium difficile* · *Salmonella* Heidelberg · *Campylobacter jejuni* · *Cryptosporidium*

Introduction

The exact incidence rate of diarrhoea in the elderly is not available but it is greater than in young adults. Diarrhoea can be mild or severe in the elderly and severe diarrhoea in the elderly can be life-threatening. It is an important cause of morbidity worldwide and is the second leading cause of morbidity [1] and mortality in the elderly [2, 3]. Deaths due to diarrhoeal illnesses occur in the elderly living in the community and in nursing homes but more so in the latter, and outbreaks have been associated with more deaths from nursing home residents [4]. A food-borne outbreak of gastroenteritis occurred in a nursing home caused by *Salmonella* Heidelberg and *Campylobacter jejuni* [5]. Another outbreak of *Clostridium difficile* infection (CDI) in a tertiary hospital in Costa Rica had been reported; the mean age of the patients was 65.5 years [6]. Outbreak of

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_14

cryptosporidium infection has occurred in elderly nursing home residents [7]. In a Rhode Island hospital, a review of 36 patients with a mean age of 77 years were identified with *Cryptosporidium* infection [8]. Fifty percent of deaths due to diarrhoea occur in individuals over the age of 75 years. In the United states, there are two different epidemiological patterns in the occurrence of viral gastroenteritis, as outbreaks in people of all ages and endemic in children [9]. There is a higher incidence of infectious and iatrogenic diarrhoea in the elderly [2], and in the elderly, drug therapy is one of the commonest causes of diarrhoea [10].

Clostridium difficile is the most common cause of nosocomial diarrhoea and disproportionally affects the elderly and in those above the age of 65 years [11, 12] and remains a disease of the elderly [12]. CDI has been increasing in frequency and in severity in the last 10–15 years [13]. This has been linked to an epidemic CD strain now known as NAP1/027 (North American pulsed-field type 1 and ribotype 027, using polymerase chain reaction) [14–16]. The elderly are particularly prone to have recurrence, treatment failure and increased mortality from CDI [17–19]. The incidence of CDI increases with age [20, 21]. Age and systemic antibiotics [22] are the two notable risk factors followed by gastric acid-suppressive medications [23–25]. Proton pump inhibitors and the H2-receptor agonists have been shown to be risk factors for the development of CDI [23–25]. Aged care facilities are often cited as a risk factor acquiring CDI [26].

The elderly are at increased risk of dying from dehydration and electrolyte abnormalities and impaired mobility and are frequently institutionalised. It is likely that deficits in both immune and non-immune defences may play a role in gastrointestinal infections in the elderly [27]. Mucosal injury results in disruption of the absorptive and secretory mechanisms both in the large and small intestine. Decreased absorption and increased secretion due disruption of the balance result in diarrhoea [28]. It largely caused by infection or inflammation. Infection causes diarrhoea by mucosal adherence, invasion or toxin production [29]. The causative agent, for example, bacteria, may adhere to specific receptors on the mucosa causing a watery diarrhoea [30] or invade the mucosa and damage the epithelial cells and vascular endothelium causing a bloody diarrhoea or producing toxins, enterotoxin and cytotoxin [29]. The former is giving rise to a watery diarrhoea and the latter a bloody diarrhoea. Infection with toxin-producing strains gives rise to a spectrum of illness [12]. It would be useful to divide diarrhoea into acute and chronic. It is acute if present for less than 2 weeks and chronic if greater than 4 weeks in duration (Fig. 1).

Clinical Characteristics

The most common causes of diarrhoea in the elderly admitted to hospital are faecal impaction, infection and drug, and in one-third no cause is found [33]. Diarrhoea is a frequent adverse effect of drugs. Drugs disrupt several mechanisms, osmotic, secretory, mucosal and transit time. Infectious diarrhoeas in the elderly are due to bacterial, viral and enterotoxic agents and antibiotic-associated diarrhoeas. Bacterial gastrointestinal infections are caused mainly by enterotoxigenic agents, sporadic or epidemic infections and food poisoning [34]. Elderly people in long-term care are very vulnerable to infectious gastroenteritis and food-borne diseases with serious outcomes [34, 35]. Shigellosis occurs in the young, in the elderly, in patients with weak immune system and who are immune impaired and they are also most likely to develop serious illness with *Campylobacter*. Non-typhoidal *Salmonella* causes food-borne infection, bacteraemia and extra-intestinal infections [36, 37]. Extra-intestinal infections occurring in the elderly were associated with higher mortality and morbidity [38]. *Clostridium difficile* diarrhoea is mostly marked in elderly patients. Elderly patients are susceptible to nosocomial cryptosporidium infection due to decreased cell-mediated immunity [39].

Depending on the severity, CDI has been classified as mild, severe, fulminant and recurrent [12]. Mild disease consists of non-bloody

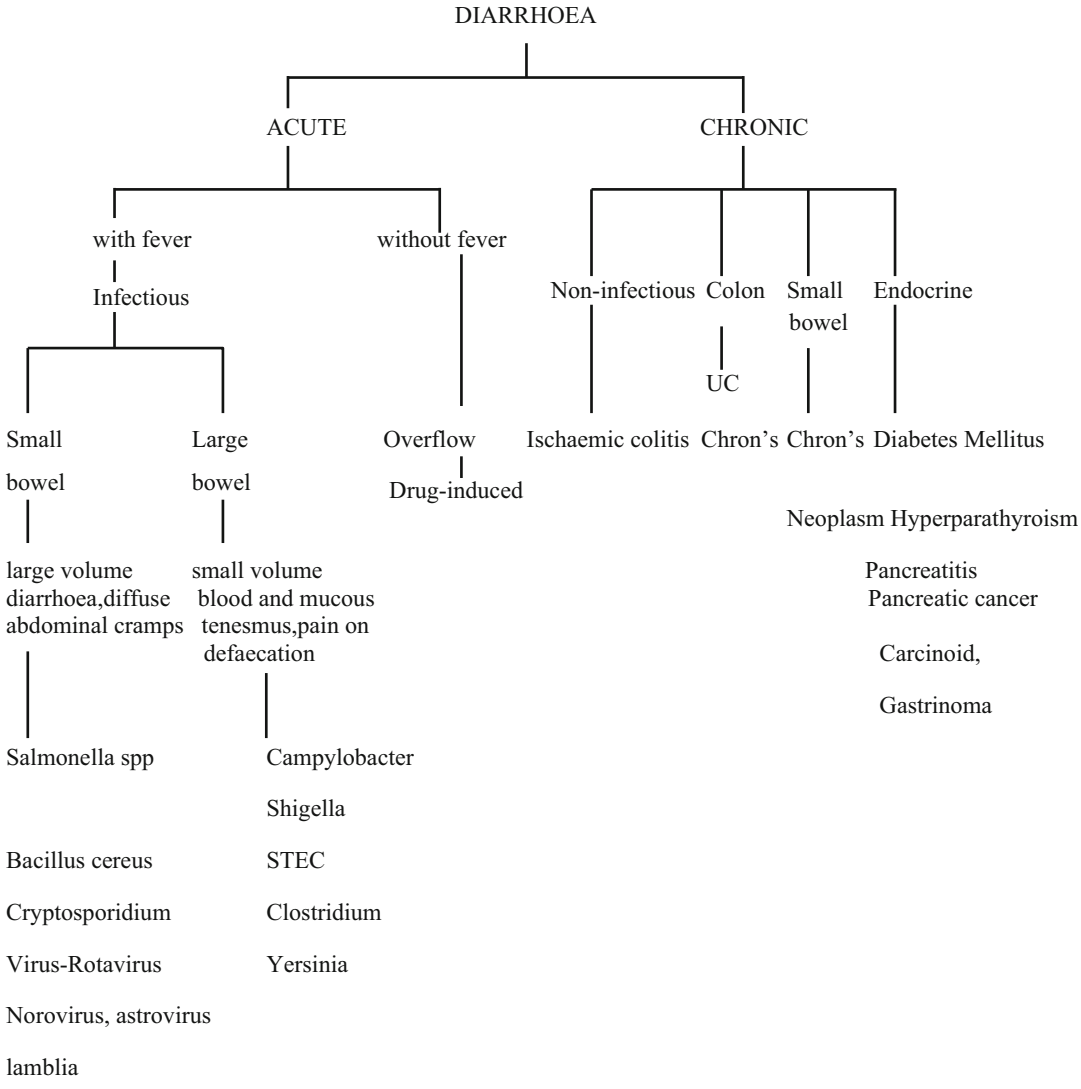

Fig. 1 Classification of diarrhoeas (Information sources: Dundas and Todd [31], Wilhelmi et al. [32])

diarrhoea and minimal systemic symptoms. In severe disease, there is profuse usually non-bloody diarrhoea and systemic symptoms such as fever malaise, abdominal pain and loss of appetite [14]. In fulminant CDI apart from systemic toxicity, there may be ileus, toxic megacolon, bowel perforation, pseudomembranous colitis and sepsis [12]. Recurrent CDI occurs in 15–30% of cases either due to relapse or to reinfection [40] and occurs within 1 month of successful treatment [12]. Real-time polymerase chain reaction is a sensitive test for CDI although false-positive results are a concern [41]. The standard diagnostic test for CDI is laboratory analysis of stool samples [42]. Although stool culture is highly sensitive, the specificity is low [42]. Cell toxicity assay has high sensitivity but is not as sensitive as stool culture [43]. In Australia and in some European countries, the diagnostic tests used are culture followed by cell toxicity assay [44]. Distinguishing characteristics of acute infectious diarrhoeas are shown in Table 1.

Table 1 Characteristics of acute infectious diarrhoeas

Organism	Transmission	Incubation	Symptoms	Diagnosis	Complications
Bacterial					
Salmonella	Infected meat poultry, dairy products, eggs, direct and indirect contact with animals	12–48 h	Watery stools, fever, crampy abdominal pain, focal manifestations	Isolating organism from stool blood culture	Endovascular infection, bacteraemia infected
Clostridium	Acquired in hospital broad-spectrum antibiotic, indirectly faecal-oral route	4–9 days	Mild to severe watery to bloody stool necrotising colitis	Assaying *C. difficile* toxin in stool rapid enzyme immunoassay	Hypovolaemic shock, toxic megacolon, pseudomembranous colitis, sepsis perforation
Shigellosis	Direct faecal-oral, indirect contaminated food	1–4 days	Mucous, pus and blood fever	Stool culture	Secondary bacterial infections, toxic neuritis, arthritis, myocarditis
Shiga toxin	Undercooked beef, water contaminated with cow manure	24 h	Bloody diarrhoea, severe abdominal cramps	Stool cultures	Haemolytic-uraemic syndrome (HUS) TTP
Campylobacter	Raw uncooked meat, poultry, linked with fast food	2–5 days	Abdominal pain, bloody diarrhoea	Blood culture and body	Septic thrombophlebitis, endocarditis, osteomyelitis
Viral[a]					
Rotavirus calicivirus, astrovirus enteric adenovirus	Variety of routes faecal-oral, route, aerosol, food-borne	1–3 days 1–3 days 8–10 days	Watery diarrhoea, abdominal cramps	Viral cultures	
Parasitic					
Cryptosporidium	Zoonotic spread	7 days	Profuse watery	Identifying	
	Waterborne, direct person-to-person contact		Diarrhoea, abdominal cramps	Acid-fast oocysts by phase contrast microscopy	

Information sources: Diggs and Surwicz [12], Dundas and Todd [31], Davis et al. [45], Blaser et al. [46], Acheson and Allos [47], Nachamkin et al. [48], Rees et al. [49] and Niyogi [50]
[a]Usually affects children but could affect all ages

Treatment

Most of the diarrhoeas are self-limiting and the treatment is mainly supportive. The differential diagnosis includes the exclusion of faecal impaction, laxative abuse, antibiotics and inflammatory bowel disease. The diarrhoea should be investigated: (i) if it has not settled within 48 h, a stool culture for parasites, cysts and ova should be done ideally on three different days; (ii) if recently hospitalised or had been on broad-spectrum antibiotics in the previous 6 weeks, the stool should be checked for C*lostridium difficile*; and (iii) if there is systemic involvement with bloody diarrhoea and (iv) if the diarrhoea persists for more than 5 days, food poisoning should be excluded.

The causes of the diarrhoeas are diverse and can be a symptom of various diseases [51] and the cause has to be specifically treated, but more frequently

Table 2 Treatment

Organism	Management
Salmonella	Fluid and bland diet, ciprofloxacin 500 mg q12h for 3–5 days, those with bacteraemia 4–6 weeks, no clinical benefit with antibiotic therapy, may increase adverse effect
Clostridium difficile	Oral metronidazole 400 mg 8 h for 10–14 days for mild cases, vancomycin 125 mg 6 h for 10–14 days in severe cases. In complicated cases, 500 mg metronidazole IV or vancomycin 500 mg 6 h orally
Shigellosis	TMP q12h, norfloxacin 40 mg bid, ciprofloxacin 500 mg po bd or norfloxacin 800 mg as single dose and ciprofloxacin 1 g as single dose
Shiga toxin-producing *Escherichia coli*	Supportive care, antibiotics to be avoided especially in patients with acutely infected producing *E. coli*
Campylobacter	Ciproflocaxin 500 mg tid-5 days, azithromycin 500 mg daily for 3 days or 30 mg/kg as single dose. Erythromycin for 5 days
Cryptosporidium	No effective drug is available but paromomycin (500–750 mg po qid) has high success rates

Information sources: Jump [13], Acheson and Allos [47], Dryden et al. [52], Sirinavin and Garner [53], Cohen et al. [54], Onwanezobe et al. [55], Vukelic et al. [56], Bhattacharya and Sar [57], Googame [58], Flanigan Sloane [59]

symptomatic treatment will be necessary. The general rule is to prevent dehydration. In the mild cases, oral hydration may be sufficient. In the more severe cases with or without nausea and/or vomiting, intravenous fluids and electrolyte replacement may be required to correct dehydration and electrolyte abnormalities. Severe dehydration and electrolyte abnormalities commonly occur in the elderly. The treatment of non-infectious diarrhoea is mainly supported with fluid replacement. In diarrhoea resulting from drug therapy, the offending drug should be avoided. The faecal flora in the elderly are very sensitive to changes by antibiotics resulting in an overgrowth of toxin-producing organisms such as *Clostridium difficile* normally suppressed by organisms such as *Escherichia coli* and *Bacteroides* in the gut. It is especially common in elderly people on chemotherapy for malignancy [9]. Infectious diarrhoeas are treated with appropriate antibiotics (Table 2). In the high-risk groups with the clinical picture of dysentery, it is justified for empirical treatment with antibiotics. Regardless of what the pathogen is, treatment with ciproflaxin 500 mg bd has shown a significant reduction in the duration and other symptoms [51]. Bacteriotherapy with faecal transplantation has shown much promise in the management of recurrent CDI [41]. Patients with toxic megacolon, perforation or shock require surgical intervention despite maximum medical therapy [12]. Prevention is largely infection control and judicious use of antibiotics, shorter duration of therapy and the use of antimicrobials with narrowest spectrum of activity [12].

Impact

Infectious diarrhoea can have disastrous results in the elderly [4] and is associated with high mortality [34]. Polypharmacy, malnutrition, multiple pathologies and residence in aged care facilities contribute to the increasing incidence and seriousness of diarrhoeas in the elderly [34]. Dehydration is especially dangerous in the elderly, and the elderly are more prone to electrolyte abnormalities. The elderly are particularly disposed to have recurrence, treatment failure and increased mortality from *Clostridium difficile* [17–19] (Box 1).

Box 1 Key Points: Diarrhoeas

The most common causes of diarrhoea in the elderly admitted to hospital are faecal impaction, infection and drug and in one-third no cause is found [33].

Fifty percent of deaths due to diarrhoea occur in individuals over the age of 75 years.

The most common causes of diarrhoea in the elderly admitted to hospital are faecal

(*continued*)

Box 1 Key Points: Diarrhoeas (continued)
impaction, laxatives and drug, and in one-third no cause is found.

Clostridium difficile is the most common cause of nosocomial diarrhoea and disproportionally affects the elderly and in those above the age of 65 years [11, 12] and remains a disease of the elderly [12].

Age and systemic antibiotics [22] are the two notable risk factors for *C. difficile* followed by gastric acid-suppressive medications [23–25].

Recurrent CDI occurs in 15–30% of cases either due to relapse or to reinfection [40].

Regardless of what the pathogen is, treatment with ciproxacin 500 mg bd has shown reduction in the duration and symptoms [51].

Fifty percent of the deaths due to diarrhoea occur in individuals over 75 years.

Clostridium difficile is the most common cause of nosocomial diarrhoeas and disproportionally affects the elderly and in those above the age of 65 years [11, 12].

Depending on the severity, CDI has been classified as mild, severe, fulminant and recurrent [12].

In fulminant CDI apart from systemic toxicity, there may be ileus, toxic megacolon, bowel perforation, pseudomembranous colitis and sepsis [12].

Multiple Choice Questions

1. The following in relation to diarrhoea are true except:
   A. If the individual had been recently hospitalised or had been abroad in the previous 6 weeks, the diarrhoea should be investigated.
   B. In the diagnosis of diarrhoea in the elderly faecal impaction, laxative use, antibiotics and inflammatory disease should be excluded.
   C. In more than half the cases in the elderly, the cause is not found.
   D. Fifty percent of the deaths due to diarrhoea is in the over 75-year age group.
2. The following are true of *Clostridium difficile* except:
   A. *Clostridium difficile* is the most common cause of nosocomial diarrhoeas.
   B. *Clostridium difficile* diarrhoea is mostly marked in young patients.
   C. If recently hospitalised or had been on broad-spectrum antibiotics in the previous 6 weeks, the stool should be checked for *Clostridium difficile.*
   D. 15–30% of cases recur either due to relapse or to reinfection.

MCQ Answers

1 = C; 2 = B

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Part IV

Liver Diseases in the Elderly

Aging is associated with both functional and structural changes in the liver. Liver volume decreases with age so does the blood flow. Part IV provides an overview of the prevalence and clinical manifestations of viral hepatitis and highlights the improvements that have occurred in clinical care. The review also discusses the prevalence and mechanisms underlying chronic liver diseases in the elderly followed by one of its complications, ascites. Viral hepatitis is a common and important infectious disease in the world today and is as common in the temperate countries as it is in the tropics. Viral infections are the commonest cause of chronic liver disease which includes alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), autoimmune hepatitis, drug-induced hepatitis, and metabolic diseases such as alpha-antitrypsin deficiency. The prevalence of chronic liver disease is increasing in the elderly. More than two-thirds of all patients with liver disease in the Western world are due to alcoholic liver disease. Almost half a million people have the hepatitis C virus in the UK. There are no age-related liver diseases, but the clinical course in the elderly differs in several aspects from those of younger adults. NAFLD is one of the most common liver disorders seen by the primary care physician. Autoimmune hepatitis occurs uncommonly in the elderly; nevertheless, there have been several studies in the elderly. Drug-induced liver injury embraces a spectrum of clinical disease ranging from asymptomatic, liver test abnormalities to acute liver failure and to a lesser extent chronicity. Primary biliary cirrhosis is now recognized more frequently than previously because of the increased awareness of the condition and the availability of diagnostic tools leading to earlier diagnosis. Provided hereditary hemochromatosis is detected early and treated, the life expectancy can be normal before cirrhosis occurs. Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide.

Viral Hepatitis in the Elderly

21

Contents

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_23

Abstract

Viral hepatitis is an inflammation of the liver caused by six viruses, called hepatitis A, B, C, D, E and G. The review provides an overview of viral hepatitis, prevalence with the main focus on their effects and/or adverse effects. Hepatitis A virus (HAV) has a worldwide distribution and is related to the hygienic and sanitary conditions of the region. Hepatitis B is of worldwide concern, is the most common cause of chronic liver disease and is highly infectious. Chronic hepatitis B usually occurs in people who have been infected at an early age. Hepatitis C has been the most frequent cause of acute hepatitis in older people. Most of the elderly with chronic hepatitis C virus infection have acquired the disease earlier in life, and they will present with complications of liver disease mainly cirrhosis and hepatocellular carcinoma. About 5% of HBV carriers are anti-HDV positive worldwide. Hepatitis G is often found as a co-infection with other viruses, the hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV).

Keywords

Hepatitis A · Hepatitis B · Hepatitis C · Hepatitis D · Hepatitis E · Hepatitis G

Introduction

Viral hepatitis is an inflammation of the liver caused by six viruses called hepatitis A, B, C, D, E and G. Viral hepatitis is a common and important infectious disease in the world today and is as common in the temperate countries as it is in the tropics. It is well known that viruses which do not normally produce liver damage with jaundice may occasionally produce a clinical picture akin to hepatitis, among them being the cytomegalovirus, herpes simplex, Coxsackie, yellow fever and others. These viruses can cause acute disease with symptoms lasting for several weeks with jaundice, nausea, vomiting and abdominal discomfort. Accordingly, it would be less confusing to refer to hepatitis as hepatitis A, hepatitis B and so forth.

Hepatitis A virus (HAV) has a worldwide distribution and is related to the hygienic and sanitary conditions of the region. In countries with high standards of sanitation, HAV antibodies are found in 50% or more in the elderly over the age of 50 years as compared to children [1]. The prevailing HAV antibodies were 40%, 60% and 80% at ages 60, 70 and 80 years, respectively, in a serological survey in the United States [2]. The elderly are at greater risk of severe effects of the illness and the fatality rate increases with age [3]. The median length of stay was longer for those 50–60 years and over than for the younger age groups [4]. A large proportion of the adult population in non-epidemic countries are not immune to the HAV infection [5].

Of the two billion people who have been infected with hepatitis B virus (HBV), 350 million have chronic lifelong infections and have a high risk of developing chronic hepatitis, cirrhosis of the liver and hepatocellular carcinoma killing about one million persons each year [6]. There are at least 320,000 deaths per year due to hepatitis B virus [7]. A recent survey showed the prevalence of HBV in Australia is rising, an estimated seroprevalence of 2.1%, and this is attributed to immigration from endemic areas such as Asia and sub-Saharan Africa [8]. Although acute hepatitis B and C are more commonly recognised in younger adults, acute infection can occur in the elderly [9]. Chronic infection is prevalent in elderly patients and may be more symptomatic and severe than in younger adults. Hepatocellular carcinoma is a serious complication of chronic HBV infection.

Hepatitis C virus (HCV) is more prevalent than HBV infection [10]. HCV previously known as non-A, non-B hepatitis occurs worldwide, and each year three to four million people are newly infected and an estimated 170 million, that is, 3% of the world population, are chronically infected [6]. Hepatitis C has been the most frequent cause of acute hepatitis in older people [4, 11]. It is the most commonly notified disease in Australia, and in 1998, the Hepatitis Virus Projections Working Group (HCPWG) estimated that approximately 210,000 people would have been infected by the hepatitis C virus by 2001 [12]. Hepatitis D virus (HDV) may occur as a co-infection with the

hepatitis B virus or as a superinfection in individuals with existing chronic HBV infection. Hepatitis E (HEV) has been described in a number of countries. Epidemics and sporadic cases are known to occur in several countries in Asia and Middle East, but no outbreaks have been recorded in Europe, the United States and Australia.

HEV IgG seroprevalence was 4% in a study of 77 patients in New Zealand, and data suggest that subclinical and unrecognised infection is common [13]. One of the cases was misdiagnosed initially as a drug reaction. It has been suggested that all patients with unexplained hepatitis whatever their age or travel history should be tested for HEV [13]. Hepatitis G (HGV) has been identified between 1 and 2% of blood donors in the United States [14] and has been associated with liver disease in older people [5]. Table 1 shows some of the characteristic of acute viral hepatitis.

Hepatitis A (HAV)

Hepatitis A is caused by a small RNA enterovirus of the picornavirus family. It is highly infectious and spreads easily in epidemics. There have been a number of waterborne and food-borne outbreaks especially to seafood from polluted water. It is transmitted by faecal-oral route by the ingestion of contaminated food, milk or water and can be transmitted sexually. It is a mild illness and death is rare. Children and young adults are more likely to become infected than the elderly. The morbidity and mortality from hepatitis A virus (HAV) infection increase with age [5, 9].

Symptomatology

There are significant differences in the manifestations of viral hepatitis in the elderly compared to younger individuals. HAV infection is more severe in the elderly. There may be no symptoms or symptoms may be minimal. The onset is usually abrupt with malaise, lethargy, loss of appetite, nausea, vomiting, fever and pain in the right hypochondrium. Diarrhoea occurs in more than half of the patients. The stools may be light pale and the urine dark. The acute illness usually lasts from one to several weeks. The course of the illness in the elderly is often problematic [15]. In the adults, the convalescence is prolonged and fulminant hepatitis which may be fatal occurs almost exclusively in the older patient, and there is a higher prevalence of fulminant hepatitis in this age group [5]. In the elderly, the poor outcome has been

Table 1 Characteristics of acute viral hepatitis

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E	Hepatitis G
Marker	IgM antiHA	HBsAg	Anti-HCV	Anti-HDV	Anti-HEV	DNA test
Major transmission	Faecal-oral	Blood and blood products	Blood and blood products	Blood and blood products	Water	Blood products
Incubation period (days)	15–50	50–180	20–120	30–180	15–60	Unknown
Severity	Mild	Mild	Subclinical	Severe co-infection	Severe	Mild
Chronicity	No	Yes	Yes	Yes	No	No
Liver cancer	No	Yes	Yes	Yes	No	No
Treatment	Supportive	Supportive	Supportive	Supportive	Supportive	Supportive
Specific treatment (chronic cases)		Antiviral agents	Antiviral agents			
Prevention	HAV vaccine	HBV vaccine immunoglobulin – HBIG		HBV	Immunoglobulin	Avoid risks

attributed to the decline in immune function, decline in the regenerative capacity and the coexistence of co-morbidities [16].

Several workers have shown that hepatitis A can affect more than one system. In detailed studies by Condrad et al. [17], a group of American soldiers who developed the disease in Korea demonstrated gastrointestinal, renal and haematological involvement. The elderly patient with acute HAV infection can present with severe jaundice and coagulopathy and is prone to complications such as prolonged cholestasis, pancreatitis and ascites [2]. There had been several autopsy studies on patients dying of fulminant hepatitis demonstrating involvement of the heart [18] and pancreas [19]. Neurological, haematological, myocardial, pancreatic, renal and gall bladder complications have been reported [2, 20–23].

Diagnosis

Although the aminotransferases especially alanine transferase (ALT) are elevated, the elevation does not parallel with the severity or prognosis [24]. The serological markers are shown in Table 2.

Treatment

Mainly supportive care.

Prevention

The routine immunisation of the elderly is open to question [5, 24]. In the elderly, vaccination should be considered in individuals without serological evidence of immunity to HAV [9]. Vaccination of the older frail residents in aged care facilities is confirmed [5]. Elderly travellers are susceptible to HAV, and it is recommended that the elderly traveller should be offered HAV vaccine rather than immunoglobulin [30] and this should be strictly enforced [31]. Vaccination schedule for travellers to endemic areas consists of two intramuscular injections, the second from 6 to 12 months after the first dose. Travellers can be considered protected 4 weeks after the first dose; if less than 4 weeks, they should receive additional immunoglobulin. Combined A and B vaccine should be given to those recently exposed to A and B viruses or who may be exposed.

Hepatitis B (HBV)

Hepatitis B was previously called serum hepatitis, is of worldwide concern, is the most common cause of chronic liver disease and is highly infectious. It is relatively uncommon in the geriatric age group [32]. In the developing world, most people get infected during childhood, and 5% of the people from the Middle East and Indian subcontinent and 8–10% from Africa, Asia and

Table 2 Serological markers in viral hepatitis

	Acute/active current	Past infection	Persistent/chronic	Recovery/immunity
Hepatitis A	HAV IgM	AntiHAV		HAV total antibody
Hepatitis B	HBsAg	AntiHBe	HBsAg	AntiHBs
	HBeAg	Anti HBc	HBeAg	AntiHBc +AntiHBs (natural or from vaccination)
	AntiHBcIgM			
Hepatitis C	Anti-HCV	Anti-HCV	Anti-HCV	
	HCV RNA			
Hepatitis D	Anti-HDV IgM	Anti-HDV	Co-infection or superinfection with HBV	
		HDV RNA		
Hepatitis E	HEV RNA			

Information sources: Dufour et al. [25]; Gitlan [26]; Gretch [27]; Aggarawal [28]; Adhami and Carey [29]

Pacific get chronically infected [6]. With age the percentage of carriers decreases, whereas the frequency of chronic disease increases. Hepatitis B virus is transmitted by blood, blood products and body fluids of an infected person. It is sexually transmitted and via the mother to the baby during delivery and child-to-child contact in household settings. Those at risk are shown in Box 1.

Box 1 HBV Groups at Risk

Day care centres (children and staff)
- Contact with patient with hepatitis
- Homosexuals
- Institutions – nursing care facilities, military barracks, prisons
- Drug users
- Travellers to endemic areas

Symptomatology

Acute Hepatitis B

The incubation period is between 1 and 4 months. The symptoms initially may be non-specific which may include fever, arthralgic pains and skin rash. Many may not have symptoms (subclinical), and others with acute hepatitis may have loss of appetite, nausea, fatigue, jaundice and pain in the right hypochondrium [33]. In an outbreak of acute HBV infection in elderly nursing home residents, a large number of those infected were asymptomatic, a smaller number had jaundice and gastrointestinal symptoms, none had to be hospitalised and there were no fatalities [34]. The symptoms usually resolve within 3 months although a very small number could end in severe liver failure. Acute hepatitis B is usually mild and is rare in older people [5]. It can be severe and the symptoms can last for several weeks or months. Less commonly (<1%), it can be life-threatening – *fulminant hepatitis* – and in the United States, the fatality rate due to fulminant hepatitis is approximately 0.2% (1 in 200) [28]. Most people recover without any sequelae, but in about 5% of the adults, the virus continues to replicate over many years and become *carriers*, and the liver damage associated with the long-standing infection is referred to as *chronic hepatitis*.

Chronic Hepatitis B

Chronic hepatitis B usually occurs in people who have been infected at an early age. The symptoms could vary widely. Many who carry the virus are asymptomatic; others have symptoms of ongoing liver inflammation that of fatigue, lethargy and loss of appetite. Some however could have a sudden worsening of the symptoms temporarily. About a fifth of the patients may show signs of extrahepatic involvement, vascular and renal [35–37]. The risk of progression to chronicity is inversely related to age at the time of infection, and the rate is higher in the elderly than in younger adults [9]. Approximately 5% that develop chronicity [28] are at greater risk of developing significant and potentially fatal disease [38]. About 10–25% progress to cirrhosis and hepatocellular carcinoma [39, 40]. Patients who develop cirrhosis or hepatocellular carcinoma may complain of fatigue, weight loss, ascites and bleeding, among others.

Diagnosis

The diagnosis of hepatitis B is on a detailed history, physical examination and appropriate diagnostic tests. The medical history should include country of birth, family history, drug use, unprotected sexual intercourse and any symptoms. In acute hepatitis, the findings on physical examination include fever, rash and tender palpable liver. In chronic hepatitis B, there may be no abnormal findings or the patients may exhibit signs of advanced liver disease.

Diagnostic Tests

I. Liver function tests. In acute hepatitis, the alanine transferase (ALT) and aspartate transaminase (AST) are usually elevated, the former higher than the latter [24], and in most people return to normal within 1–4 months.

The persistence of ALT beyond 6 months suggestive of developing chronic hepatitis and the enzyme levels could vary from normal to a few hundreds (40–1,000 IU/L). The serum bilirubin is elevated. A low albumin suggests chronic liver damage and a prolonged prothrombin time severe liver damage.

II. Hepatitis markers. A number of antigens are associated with the virus, and each antigen may result in related antibodies. HBsAg indicates the presence of the virus, and its antibody antiHBs denotes that the patient is immune and the virus may be cleared. HBcAg is never detectable in the serum, and the antibody antiHBc (core antibody) signifies that the patient has come into contact with hepatitis B and may or may still not be infected with the virus nor does it signify immunity. IgM antiHBc signifies recent contact with hepatitis B, and if only the IgG antibody is detected, the infection occurred at least 6 months prior to the test. HBeAg indicates active virus replication and ongoing liver disease and the person is infectious, and its antibody, antiHBe, reduced replication and inactive liver disease and patient is less infectious [27, 28] (Table 1).

Although generally less mild than HAV, HBV carries a high mortality. Those who are chronically infected develop varying degrees of chronic hepatitis, cirrhosis of the liver and hepatocellular carcinoma. HBV is responsible for the increased number of hepatocellular cancer (HCC) even in low-to-medium prevalence areas such as Australia [41]. Approximately 60% of the HCC worldwide is associated with chronic HBV infection [42]. HCC is almost always fatal and usually develops between 35 and 65 years of age [6]. The virus may persist in the liver for years, and the clinical outcomes are determined therefore by the viral replication cycle and the host immune responses. Complete eradication of the virus is not possible, and treatment efficacy is gauged by the ability to limit HBV replication before significant irreversible damage occurs [43]. The frequency of clinical disease increases with age but the percentage of carriers decreases [38].

Management and Treatment

It is preventable with safe and effective vaccines being available. Although the vaccine will not cure chronic hepatitis, it is 95% effective in preventing chronic infections from developing [6]. Two major classes of antiviral therapeutic agents for the treatment of chronic hepatitis B are immunomodulators (interferon alfa, thymosin alpha 1, therapeutic vaccines) and nucleoside analogues (lamivudine, adefovir, entecavir, emtricitabine) [44]. Patients with chronic HBV infection and evidence of active replication are given alpha-interferon to prevent progression of the disease [45]. Effectiveness of the therapeutic regimes is assessed by the sustained suppression of HBV DNA, normalisation of transaminase levels and a stable stage of HBsAg seroconversion with persistence of circulating antiHBeAg antibodies [43].

Hepatitis C (HCV)

HCV has a long incubation period (median 50 days) and is prevalent in intravenous drug users and haemodialysis and haemophilia patients. Sexual transmission appears to be uncommon as only 8% of HIV-positive male homosexuals tested positive for hepatitis C antibodies (see Box 2). The main significance is that it is strongly associated with development of chronic liver disease. It is the most frequent cause of acute hepatitis in the elderly [2, 5, 11], and after 20–30 years, about half the number develop chronic hepatitis [24], and of those a significant number develop cirrhosis (20–60%) [48] and a small percentage liver cancer. It is the cause of half of the cases of primary cancer of the liver in the developed world. Most of the elderly with chronic hepatitis C virus infection have acquired the disease earlier in life, and they will present with complications of liver disease mainly cirrhosis and hepatocellular carcinoma [49]. The risk of hepatocellular carcinoma will increase with age probably due to age-related changes in the ability to repair DNA [50] (Fig. 1).

Box 2 HCV Risk Factors

Injecting drug use, needle-sharing
Transfusion prior to 1990
Needle-stick injury
Sharing of toothbrushes and razors
Renal dialysis
Tattoos, body piercing, circumcision
Born outside Australia
Multiple sexual partners, unprotected sex
History of previous sexually transmitted diseases

Information sources Terrault [46], Yee et al. [47]

Symptomatology

Acute hepatitis C is generally benign; less than 25% are estimated to be icteric. Largely asymptomatic, a small percentage of patients however may develop a range from mild to severe early symptoms which include fever, headaches, nausea, vomiting, general malaise and diarrhoea and later develop abdominal pain, jaundice [51], tenderness in the right hypochondrium and clay-coloured stools. 10–20% of them clear the virus in 2–6 months.

Chronic C hepatitis: about 80% of the newly infected progress to develop chronic infection. Many of them are asymptomatic for long periods of time. The elderly with chronic HCV often present with decompensated cirrhosis or hepatocellular cancer as initial manifestations [52]. Others may have symptoms of malaise, fatigue and lethargy, intolerance to alcohol and discomfort in the right hypochondrium and develop signs of chronic liver disease. 10–20% develop cirrhosis of the liver and 1–5% liver cancer over a period of 20–30 years [6].

Diagnosis

Diagnostic tests are divided into two categories: (1) serological assays and (2) molecular assays [29, 53]. Serological testing for anti-HCV antibodies includes measurement by immunoassay (EIA) and supplemental tests such as the recombinant immunoblot assay (RIBA) [29, 53]. The EIA-3, the third-generation test, is more sensitive. The ideal approach is to test for HCV RNA by using a sensitive assay such as polymerase chain reaction (PCR) [29], and a positive HCV RNA indicates active infection. It is more likely the elderly with HCV RNA viraemia to have normal ALT levels compared to younger adults [54]. The ALT may be normal on multiple occasions in about 40% of the patients with hepatitis C, and the diagnosis should be established by HCV RNA. The serological markers for fibrosis may be useful in the elderly especially with normal ALT levels for the assessment of fibrosis [52]. The most sensitive test for determining the hepatitis C viral load is the quantitative PCR [29]. The differential diagnosis includes a number of conditions such as chronic hepatitis B and D, alcoholic hepatitis, non-alcoholic steato-hepatosis (NASH), auto-immune hepatitis and drug-induced liver disease.

Management

The pegylated form of interferon alpha is the mainstay of treatment and is a potent inhibitor of HCV replication [55]. A combination of peginterferon and ribavirin is an effective treatment for hepatitis C. Treatment is usually given for 6–12 months with regular follow-up by the specialist and the primary care physician. Other agents used are telaprevir and boceprevir. The response rate is improved by adding these to peginterferon and ribavirin. Another antiviral drug sofosbuvir can be added to the combination treatment for chronic hepatitis [56]. Recently, a combination of two direct-acting antivirals, sofosbuvir and ledipasvir, in a single tablet taken once a day for 12 weeks had been shown to cure >95% of treatment-naïve HCV genotype 1 patients largely with little side effects [57]. Testing for the HCV genotyping is clinically important. There are multiple known genotypes and subtypes of hepatitis C [58]. And there are six major types. Genotype 1 is the

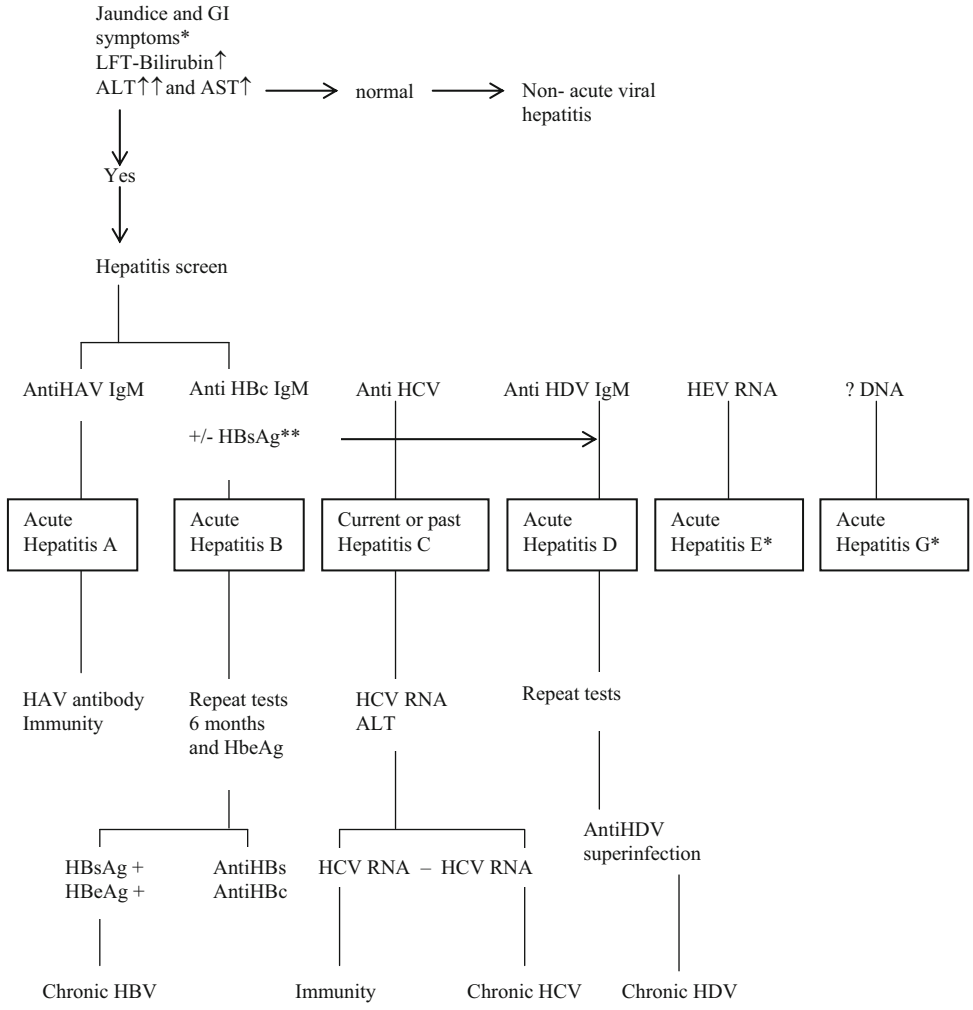

Fig. 1 Algorithm in viral hepatitis. *HBsAg every year if still a carrier; alpha-fetoprotein (AFP) every 6 months; HBeAg yearly; ultrasound of liver/yearly. AST, ALT and GGT and liver biopsy to assess severity of the disease in relation to necroinflammation and fibrosis. + = positive; = negative. * GI symptoms: nausea, vomiting, loss of appetite, constipation or diarrhoea. **The diagnosis of hepatitis D should be considered if positive HBV infection is present, that is, a positive serum HBsAg or HBV DNA or both

commonest in about half of the cases, followed by genotype 3. Patients with genotype 2 and 3 are two or three times more likely to respond to interferon therapy than those with genotype 1 [58]. The risk-benefit of antiviral therapy for the elderly patient with hepatitis C should be assessed on an individual basis. Although it has been shown that age is an independent factor for poor response to treatment, it has been recommended that patients up to the age of 75 years be included in trials of hepatitis C treatment [49].

Hepatitis D (HDV)

HDV virus is a defective RNA particle that is totally dependent on HBsAg to enter the liver cells [31]. HDV is spread by blood products, sharing drugs [31], needles, needle-stick injury,

infected mother to baby and sexual transmission. About 5% of HBV carriers are anti-HDV positive worldwide [31].

Symptomatology

The incubation period is between 30 and 180 days. Onset is with fatigue, loss of appetite, nausea, vomiting, joint pains, abdominal discomfort and jaundice. Patients with HBV-HDV co-infection may have a more severe acute illness and a higher risk of developing acute liver failure compared with HBV infection alone [59]. Those with HDV superimposed on chronic carriers with HBV infection develop chronic HDV infection and could progress to cirrhosis of the liver or hepatocellular carcinoma.

Diagnosis

The diagnosis is by specific serological testing for anti-HDV antibodies. The diagnosis of hepatitis D should be considered if positive HBV infection is present, that is, a positive serum HBsAg or HBV DNA or both [31].

Management

Prevention

Hepatitis B vaccination, pre- or post-exposure prophylaxis (hepatitis B immune globulin or vaccine are given) to prevent HDV infection. To reduce HBV-HDV superinfection, individuals with chronic HBV infection should be educated about risk behaviours. In those with acute HDV infection, there is no treatment other than supportive care. Chronic HDV infection can be treated with antiviral therapeutic agents such as interferon alpha.

Hepatitis E (HEV)

As with hepatitis A, transmission is by ingestion of faecally contaminated drinking water and is highest for those who ingest food in settings of poor sanitation. HEV is endemic and epidemic in Asia, Africa and Mexico and is sporadic in Western Europe and the United States [9]. Very little is known of acute infection with HEV in the elderly, but the seroprevalence of HEV IgG antibodies has been reported to increase with age [9]. According to Carrion and Martin [9], in the elderly it should be considered a likely cause of acute hepatitis.

Symptomatology

The incubation period is between 15 and 60 days. Symptoms are that of fatigue, loss of appetite, nausea, abdominal pain and fever. It is a self-limiting disease with a low case fatality rate in the general population but is higher in pregnant women [33]. Fulminant hepatitis is more commonly associated with HEV than with other hepatitis [56]. Chronicity does not occur.

Diagnosis

Serological testing for anti-HEV antibodies.

Management

Vaccine against HEV is not available. Immunoglobulin prepared from plasma collected in HEV-endemic areas had not been effective. The best prevention is using measures recommended for hepatitis A [60].

Hepatitis G (HGV)

HGV is a single-stranded virus belonging to the *Flaviviridae* family and designated GB virus (GBV-C) and hepatitis G virus (HGV) [61, 62]. It is transmitted parenterally and probably sexually [61]. It is often found as a co-infection with other viruses, the hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV). In the United States, 10–20% of HGV patients are co-infected with HCV [33] and HBV and appear not to influence the outcome

of HCV- and HBV-related liver disease [60]. HGV has a protective role in HIV patients [63]. In an Italian study, HGV infection was highly prevalent in the population studied, and the cumulative risk exposure was proportional to age [64]. There was a high prevalence of HGV infection [65] compared to HCV in patients undergoing haemodialysis [66]. However, only 0.3% of persons with acute viral hepatitis are infected with GBV-C/HGV alone [62].

Symptomatology

Almost all cases are asymptomatic. There is some evidence that patients could carry the virus for several years. Carrier rate is between 2 and 5% in the general population.

Prognosis

Little is known but said to be mild.

Management

Prevention

Avoidance of contact with contaminated blood and blood products.

There is no specific treatment.

Figure 1 suggests an algorithm for the evaluation and diagnosis in viral hepatitis.

Impact

Chronic lifelong HBV infections have a high risk of developing chronic hepatitis, cirrhosis of the liver and hepatocellular carcinoma killing about one million persons each year [6]. Chronic hepatitis B and compensated cirrhosis have a moderate impact on HR-QoL and, when associated with decompensated cirrhosis and hepatocellular carcinoma, has an enormous deleterious effect on QoL [67]. There is an increasing volume of literature on the impact of hepatitis C on QoL. It is the most frequent cause of acute hepatitis in the elderly [2, 5, 11], and after 20–30 years, about half the number develop chronic hepatitis [24] and of these a significant number develop cirrhosis (20–60%) [48] and a small percentage liver cancer. It is associated with enormous clinical, economic and quality of life burden [68]. Several studies have demonstrated a significant decreased QoL in patients with hepatitis C. The HR-QoL is reduced in hepatitis C patients even in the absence of cirrhosis, and treatment has shown improvement in the HR-QoL with successful treatment [69]. Hepatitis C infection and its management have a significant impact on health and social well-being [70]. Fatigue, depression, sexual dysfunction and neurocognitive deficits are common complaints with chronic hepatitis C infection and have an extreme effect on HR-QoL [71] (Box 3).

Box 3 Key Points: Viral Hepatitis

The elderly patient with acute HAV infection can present with severe jaundice and coagulopathy and is prone to complications such as prolonged cholestasis, pancreatitis and ascites [2].

Elderly travellers are susceptible to HAV, and it is recommended that the elderly traveller should be offered HAV vaccine rather than immunoglobulin [30].

There is a high rise of hepatitis B among immigrants from endemic areas. Chronic hepatitis B usually occurs in people who have been infected at an early age.

The risk of progression to chronicity is inversely related to age at the time of infection, and the rate is higher in the elderly than in younger adults [9].

Two major classes of antiviral therapeutic agents for the treatment of chronic hepatitis B are the immunomodulators (interferon alfa, thymosin alpha 1, therapeutic vaccines) and nucleoside analogues (lamivudine, adefovir, entecavir, emtricitabine) [44].

It is the most frequent cause of acute hepatitis in the elderly [2, 5, 11], and after

(*continued*)

Box 3 Key Points: Viral Hepatitis (continued)

20–30 years, about half the number develop chronic hepatitis [24] and of those a significant number develop cirrhosis (20–60%) [48] and a small percentage liver cancer.

Recently a combination of two direct-acting antivirals, sofosbuvir and ledipasvir, in a single tablet taken once a day for 12 weeks had been shown to cure >95% of treatment-naïve HCV genotype 1 patients largely with little side-effects [57].

The diagnosis of hepatitis D should be considered if positive HBV infection is present, that is, a positive serum HBsAg or HBV DNA or both [31].

Seroprevalence of HEV IgG antibodies has been reported to increase with age in the elderly; it should be considered a likely aetiology of acute hepatitis [9].

HGV is often found as a co-infection with other viruses, the hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV).

Multiple Choice Questions

1. The following in relation to viral hepatitis are true, except:
   A. Immunoglobulin administered within 2 weeks of exposure can prevent hepatitis A.
   B. Hepatitis C vaccine is available.
   C. Patients with hepatitis C with genotype 2 and 3 are two or three times more likely to respond to interferon therapy than those with genotype 1.
   D. Hepatitis B vaccination has been recommended to healthy elderly especially for those at risk of hepatitis B infection.
2. The following are true in relation to viral hepatitis, except:
   A. Chronic hepatitis B usually occurs in elderly people who have been infected at an early age.
   B. The elderly with hepatitis A are at greater risk of severe effects of the illness, and the fatality rate increases with age.
   C. The elderly with chronic HCV often present with decompensated cirrhosis or hepatocellular cancer as initial manifestations.
   D. The diagnosis of hepatitis D need not be considered if positive HBV infection is present.
3. The following are true about viral hepatitis, except:
   A. Acute hepatitis C is generally benign; less than 25% are estimated to be icteric.
   B. Hepatitis C is preventable with safe and effective vaccines being available.
   C. Fulminant hepatitis is more commonly associated with HEV than with other forms of hepatitis.
   D. HGV is often found as a co-infection with other viruses, the hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV).

MCQ Answers

1 = B; 2 = D; 3 = B

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Chronic Liver Disease

22

Contents

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_22

Abstract

The prevalence of chronic liver disease is increasing in the elderly. More than two-thirds of all patients with liver disease in the Western world are due to alcohol liver disease (ALD) and hepatitis C virus occurring alone or in combination. Viral infections are the commonest cause of chronic liver disease which includes alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, drug-induced hepatitis and metabolic diseases such as alpha-antitrypsin deficiency. There is no age-related liver diseases, but the clinical course in the elderly differs in several aspects from those of younger adults. NAFLD is one of the most common liver disorders seen by the primary care physician. Autoimmune hepatitis occurs uncommonly in the elderly; nevertheless there have been several studies in the elderly. Drug-induced liver injury embraces a spectrum of clinical disease ranging from asymptomatic, liver test abnormalities to acute liver failure and to a lesser extent chronicity. Primary biliary cirrhosis is now recognised more frequently than previously because of the increased awareness of the condition and the availability of diagnostic tools leading to earlier diagnosis. Provided hereditary haemochromatosis is detected early and treated, the life expectancy can be normal before cirrhosis occurs.

Keywords

Viral hepatitis in the elderly · Chronic liver disease · Alcoholic liver disease · Non-alcoholic fatty liver disease (NAFLD) · Autoimmune hepatitis · Drug-induced hepatitis · Hereditary haemochromatosis

Introduction

The prevalence of chronic liver disease is increasing in the elderly [1]. Over the next few years, there will be an increase in the frequency of alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) [2]. In the district general hospitals in the UK, alcohol accounts for 80% of all liver cirrhosis [3]. In England and Wales, liver disease ranks fifth as the cause of death after heart, cancer, stroke and respiratory disease [4]. In the United States, it is estimated that over two million persons have ALD [5]. More than two-thirds of all patients with liver disease in the Western world are due to ALD and hepatitis C virus occurring alone or in combination [6], and up to almost half a million people have the hepatitis C virus in the UK [7]. There are no age-related liver diseases, but the clinical course in the elderly differs in several aspects from those of younger adults [8]. In the Western world, 20–30% of the population is afflicted with NAFLD which is the most common liver problem [9]. Common causes of chronic hepatitis are shown in Box 1.

Box 1 Common Causes of Chronic Hepatitis

Viral hepatitis B, C and D
- Alcoholic hepatitis
- Non-alcoholic fatty liver disease
- Autoimmune hepatitis
- Drug-induced liver injury
- Wilson's disease/alpha-antitrypsin deficiency

Alcoholic Liver Disease (ALD)

About 10–35% of the long-term heavy drinkers develop alcoholic hepatitis, and only 8–20% progress to cirrhosis, but the majority develop fatty liver [10–12].

Symptomatology

Acute alcoholic hepatitis can occur in an alcoholic at any stage during the course of a fatty liver cirrhosis syndrome and has been described in the literature under a variety of names, namely, acute hepatic insufficiency of the chronic alcoholic, toxic hepatitis, nutritional fatty liver with

hepatocellular degeneration and acute alcoholic hepatitis. The relationship between drinking and alcoholic hepatitis is complex. In many patients it may not develop until several years of alcohol abuse, but in a few, it may appear within a year or after a binge for the first time. It may occur at any age, and the peak incidence is in individuals aged 20–60 years [13].

Alcoholic hepatitis is a syndrome with a wide spectrum of severity, and the presenting symptoms may vary. The more severe specific symptoms may include deep jaundice, prolonged prothrombin time, encephalopathy and liver failure. Clinically, the condition may be associated with constitutional disturbances such as fever, loss of appetite, abdominal pain, nausea, vomiting and jaundice of varying degree. When severe abdominal pain with vomiting is the presenting feature, it may mimic an acute surgical abdomen, and when deep jaundice is associated with abdominal pain and vomiting, a diagnosis of extrahepatic biliary obstruction may sometimes be made [14]. The severity of the disease is likely to become worse after a bout of severe drinking.

Box 2 Laboratory Findings in Acute Alcoholic Hepatitis

AST > ALT.

GGT is elevated.

Alkaline phosphatase level is increased.

Serum bilirubin increases and equates to severity.

Low albumin level.

Low serum cholesterol level.

Increased IgA and IgM levels.

Prolonged prothrombin time equates to severity.

Leucocytosis with shift to the left.

Chronic liver disease is increasing in the elderly. The spectrum ranges from fatty liver to hepatic inflammation, necrosis, with progressive fibrosis, and hepatocellular carcinoma [15]. Among patients over the age of 60 years who presented with ALD, the symptoms were more severe with increased frequency of complications of portal hypertension [16] and are the earliest and most important complication of cirrhosis [17]. The complications include portal hypertension, oesophagogastric variceal bleeding, portosystemic encephalopathy, ascites and other metabolic disturbances [18].

Diagnosis

The diagnosis of alcoholic hepatitis is based on a thorough history, physical examination and laboratory tests. Sometimes liver biopsy may be necessary to secure the diagnosis. The serum aminotransferase (AST and ALT) exhibits a characteristic pattern. The AST is moderately elevated in most patients compared with the ALT which is marginally elevated or not all in contrast to what occurs in other liver disorders. An AST/ALT ratio of more than 1 is characteristic of patients with alcoholic hepatitis. The increase in the aminotransferase levels is modest, and any increase of the AST level above 500 U/L should signal the possibility of another diagnosis or cirrhosis of any cause [13]. ALP is typically elevated, and levels 500 U/L occur in a small percentage of patients. GGT is elevated markedly by alcohol use, and a normal value helps to exclude alcohol as a cause. An elevated level does distinguish between simple alcoholism and alcoholic hepatitis. High bilirubin levels and prothrombin time reflect severity of the alcoholic hepatitis. The ultrasound demonstrates an enlarged liver which is diffuse echogenicity which is also a feature of fibrosis. The histology reveals ballooning, and necrosis of the hepatocytes with focal accumulation of polymorphonuclear cells and lymphocytes may be seen in the portal tracts together with eosinophilic hyaline inclusions termed Mallory bodies, macrovesicular steatosis, fibrosis and frank cirrhosis. The diagnosis of alcoholic cirrhosis can be made on a clinical basis in conjunction with blood tests, and liver biopsy is usually not required [19]. Box 2 shows the biochemical findings in acute alcoholic hepatitis.

Prognosis and Treatment

The 5-year survival is about 90% in patients with compensated alcoholic cirrhosis and persistent abstinence [19]. In patients with decompensated cirrhosis, the 5-year survival is 30% [19, 20]. With mild acute alcoholic hepatitis, there will be marked improvement with abstinence and supportive care. In moderate to severe alcoholic hepatitis, the use of steroids is gaining acceptance [21] with the proviso that effectiveness is evaluated at 1 week [22]. The risk of death in alcoholic hepatitis is 10–20% [23]. Abstinence is the hallmark, and nutritional therapy is the fundamental line of therapeutic intervention for ALD [22]. Pentoxifylline appears to be beneficial especially in early hepatorenal syndrome [22, 24]. Transplantation is an effective option in patients with end-stage ALD than with patients who are abstinent [21, 22, 24, 25], and the 7 year survival rate is reported as 60% in ALD, 76% in primary biliary cirrhosis and 57% in chronic hepatitis [25].

Non-alcoholic Fatty Liver Disease (NAFLD)

It is one of the most common liver disorders seen by the primary care physician [26]. Its prevalence ranges from 3% to 24% in the general population and increases with age and after menopause [27]. Seventeen percent to 35% of Americans are afflicted with NAFLD, and NASH (non-alcoholic steato-hepatitis) could present in one-third of NAFLD cases [28, 29] and is the most common liver disease in the United States [30]. NAFLD affects mainly the middle aged and the elderly [31] for with increasing age comes with more risk factors for its development [32].

Symptomatology

About 1/3 rd of patients with NAFLD develop true NASH, and only around 20–30% of NASH cases progress to cirrhosis NAFLD/NASH show progressive fibrosis in 32% and cirrhosis in 20%, and death occurs in 12% in 10 years [28]. There is a wide range of possible symptoms. Patients often present with only mild to moderate increase in the aminotransferase with no symptoms. Symptoms are non-specific; lethargy and discomfort in the right hypochondrium have been described [33]. Among clinical symptoms, abdominal discomfort as well as chronic fatigue are relatively common [28]. It was earlier considered a benign disease, but recent studies suggest an increase in mortality in the >60-year-old group [32].

Diagnosis

There is no definite diagnostic blood test for NAFLD a raised ALT is the most common abnormality in cases with NAFLD in a large percentage of cases, the ALT however can be normal and can remain normal even in the presence of fibrosis and cirrhosis. Characteristically the ALT/AST ratio is greater than 1, but this can reverse in the presence of severe fibrosis and cirrhosis. Since there is no convincing test, any obese or overweight person with mild abnormalities in the liver function tests should generate the possibility of NAFLD. Patients with insulin resistance measured by fasting insulin levels and plasma glucose levels together with central obesity, hypertension and hypertiglyceridaemia are suggestive though not specific of the diagnosis [34]. Although ultrasound (or CT) is used to diagnose fatty liver (macrovesicular fat), it is not possible to determine the extent of fibrosis and inflammation. The gold standard is liver biopsy with histological features of fibrosis, ballooning of the hepatocytes and Mallory bodies or subsinusoidal fibrosis [35]. However the histological features of NAFLD are indistinguishable from alcohol-induced liver damage [36, 37]. If there are histological features [35], then there is a risk of progression [37].

Treatment

Weight loss, exercise, diet and lifestyle changes are the mainstay of treatment [5]. Factors such

as hypertension, diabetes and hyperlipidaemia which are common in patients with metabolic syndrome have to be treated. Weight loss surgery can assist weight loss in the morbidly obese patient. The most used agent is metformin [28]. Early trials have shown that ursodeoxycholic acid and betaine appear particularly promising [30].

Autoimmune Hepatitis (AIH)

It occurs uncommonly in the elderly; nevertheless there have been several studies of AIH in the elderly [38, 39, 40, 41, 42]. In Japan the age of onset is 50 years compared to 10–12 years in the Caucasians [43]. It is classified into three subtypes [44].Type 1 has a bimodal peak 10–20 years and 45–70 years [45], and Type 2 occurs in the very young between the ages of 2 and 14 years. Type 3 occurs in adults 30–50 years, and females predominate [46].

Symptomatology

The patients may present with fever, jaundice and pain in the right upper quadrant which may resolve or progress to chronic disease or progress rapidly to acute liver failure. Many may present as chronic hepatitis from subclinical asymptomatic illness to that of a disabling chronic disease. The symptoms and physical findings stem from the various extrahepatic diseases associated with autoimmune hepatitis [47].

Diagnosis

Liver biopsy is recommended for a firm diagnosis [48]. The hallmark of AIH consists of interface hepatitis characterised by infiltration with mononuclears and plasma cells together with ballooning, hepatic regeneration with rosette formation and subsequent development of peripheral fibrosis [48]. Elevated titres of anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (anti-SMA) (Type 1), anti-liver-kidney microsomal antibodies (anti-LKM) (Type 2), autoantibodies to soluble liver proteins (SLA) or the liver pancreas antigen (LP) (Type 3) [49] are often detected. Serum electrophoresis demonstrates polyclonal hypergammaglobulinaemia; immunoglobulin G (IgG) is predominant. Aminotransferases (ALT<AST) are elevated in almost all the patients. Alkaline phosphatase and serum bilirubin are moderately elevated. In the report of the International Autoimmune Hepatitis Group, consensus diagnostic criteria were reached [50]. After excluding all other aetiological factors, the diagnostic score prior to liver biopsy was centred upon aminotransferase, gamma globulin concentrations and titres of circulating antibodies [38].

Treatment

Prednisolone and azathioprine are the mainstay of drug therapy.

Drug-Induced Liver Injury (DILI)

The overall prevalence of DILI may be as high as 10–15 cases per 100,000 patient years based on population studies [51]. In the United States, acetaminophen (paracetamol) is the most common cause of DILI [52], and 500 Americans die each year of acute liver failure due to acetaminophen [53, 54]. It is an important cause of abnormal liver tests in the outpatients [55].

Symptomatology

The presenting features of drug-induced hepatitis are variables from asymptomatic to fulminant hepatic failure. The injury may be hepatocellular with elevations of aminotransferases as predominant symptoms or cholestatic injury with elevated alkaline phosphatase [56, 57] with or without hyperbilirubinaemia, or mixed [56]. The cholestatic type increases with older age [58]. DILI patients with either type of injury with jaundice have a 10% risk of short-term mortality [51, 56]. Each drug is associated

with a characteristic signature regarding the pattern of injury, liver test abnormality, latency to symptomatic presentation and the presence or absence of immune-mediated hypersensitivity [57, 59]. Some drugs may exhibit more than one signature [59]. It manifests in most instances 5–90 days after the causative medication was last taken [56]. The severity is more with the hepatocellular type and more likely to become chronic with the cholestatic/mixed type [60].

Diagnosis

Diagnosis should include a thorough drug history with the dose, duration and past reaction to the drug. Other causes of liver injury or cholestasis have to be excluded. The most commonly implicated drugs are acetaminophen [51, 53, 54], antimicrobials [51], non-steroidal inflammatory drugs [56], statins [61], isoniazid and herbal remedies [58, 62]. A knowledge of the track record is important. A positive de-challenge is a 50% fall in the transaminase levels within 8 days of stopping the drug [63]. Liver biopsy may show spotty necrosis in the acute cases and steatosis, pigment accumulation (lipofuscin) and hepatic fibrosis and cirrhosis in the chronic hepatocellular injury. Other pathological features are that of cholestasis, granulomatous changes and vascular lesions.

Box 3 Drugs That Induce and Inhibit P-450 Enzymes

Induce	Inhibit
Phenobarbitone	Amiodarone
Phenytoin	Cimetidine
Carbamazepine	Erythromycin
Primidone	Isoniazid
Rifampin	Metronidazole
Quinine	Quinidine
	Grape fruit

Information source: Mehta et al. [63]

Primary Biliary Cirrhosis (PBC)

Annual incidence is estimated at 0.7 and 49 cases per million population and prevalence at 6–7 and 40 cases per million population [64]. Females outnumber the males by 9:1 [65, 66] with a prevalence of 1 in 1,000 women over the age of 40 years [66]. In the Netherlands, there are several thousands of patients with PBC [67].

Symptomatology

Majority of the patients are asymptomatic at the time of presentation, and common symptoms are fatigue and pruritis [66–69]. Women with PBC frequently have malabsorption, osteoporosis and autoimmune diseases.

Diagnosis

The diagnosis is based on sustained elevation of serum markers of cholestasis, namely, alkaline phosphatase, gamma G transaminase and the anti-mitochondrial antibodies (AMA).

Treatment

Ursodeoxycholic acid (UDCA) is the only currently used medication [64, 66, 68, 70]. For patients in liver failure, liver transplantation is an option, and the survival at 7 years is 70% [64].

An overview of the causes of chronic liver disease is shown in Table 1.

Hereditary Haemochromatosis

Hereditary haemochromatosis is a genetically inherited disorder. About 90% of patients with hereditary haemochromatosis in northern Europe are homozygous for a single mutation (C282Y) [71]. C282Y heterozygosity is nil in Asian, Indian subcontinent, African, Middle Eastern and Australasian populations, and in Europeans it is 9.2% [72]. A systematic review found that only 1.2% of

Table 1 Overview of the causes of chronic liver disease

	Alcoholic hepatitis	NSFLD	Autoimmune hepatitis	Drug-induced liver injury	Metabolic diseases, Wilson's disease
Risk factors	Heavy drinking	Obesity metabolic	Associated autoimmune syndrome	Drug history diseases	Family history
Age/gender years	20–60 years males predominate	Middle-age females predominate	All ages females predominate	All ages elderly more vulnerable	As late as 40
Symptoms ring severity	Symptoms-cirrhosis	Wide range chronic hepatitis	Symptoms of asymptomatic cirrhosis	Highly liver failure	Kayser Fleisher
Associated disorders		Metabolic syndrome	Autoimmune diseases		
Laboratory	AST/ALT>1<300 AP II, GGT III	ALT/AST>1200–300	AST, ALT II AP I ASMA, ANA SLA (type3) hypergammaglobulinaemia	AST, ALTI	Ceruloplasmin low Cu concentration in urine
Liver biopsy	Hepatocyte ballooning necrosis, Mallory bodies, fibrosis	Hepatocyte ballooning steatosis, Mallory bodies, fibrosis	Piecemeal necrosis, cell infiltration-plasma cells bridging necrosis	Hepatocellular or cholestatic changes	

Information sources: see text

adult C282Y homozygotes within a defined region in the United Kingdom over a 2-year period had been diagnosed with iron overload and receiving treatment [71]. In the Caucasian population, the prevalence is between 1 in 200 and 1 in 500 [73, 74].

The exact mechanisms of most of the adult haemochromatosis are unclear. In patients with hereditary haemochromatosis who are homozygous for the mutant HFE, there is a deficiency of hepcidin [75] so that iron absorption by the duodenal enterocyte continues even when the body iron stores are full. The normal level of body iron in the body is 3–4 g [76]. In haemochromatosis the level may rise fivefold. The transferrin saturation is increased, and it determines if an individual has excessive load of iron in the body. Decades of iron deposition in the organs cause tissue damage. In the liver it gives rise to cirrhosis, in the pancreas diabetes, heart cardiomyopathy, the pituitary gland manifesting as loss of libido or impotence and joints.

Clinical Manifestations

For many years the patient may be asymptomatic but for non-specific symptoms such as fatigue, malaise and joint pains with minor elevations of the aminotransferases. It is only in the fifth or sixth decade that the manifestations of organ damage appear. Manifestations include liver dysfunction and cirrhosis, glucose intolerance, arthritis, breathlessness and sexual dysfunction. The iron deposition in the skin gives it a bronze-like appearance.

Diagnosis

Excessive iron binding saturation of transferrin exceeding the normal value of 50%, serum ferritin in excess of 1,000 ngm/ml and elevation of serum liver enzymes are found in HH. A small rise of the ALT may be the first marker, and persistent ALT not due to any other cause should be investigated with measurement of fasting transferrin saturation and ferritin levels. Genetic testing is available for the C282Y mutation which can confirm the diagnosis and also can be used for screening of first-degree relatives. The demonstration of the iron content in the liver by liver biopsy is the gold standard which confirms the diagnosis, for detection of cirrhosis, to determine prognosis and the need to screen for hepatocellular carcinoma.

Screening

First-degree relatives of the individual with the condition should be screened by iron studies and genetic testing. There is a long latent period before the clinical disease manifests, and there is a good test, and screening is cost-effective [77, 78]. The transferrin saturation is used as the initial screening test followed by genotyping and clinical assessment.

Prognosis

Provided it is detected early and treated, the life expectancy can be normal before cirrhosis occurs. Hepatocellular carcinoma is about 100 times more likely to occur in haemochromatosis with cirrhosis than in healthy persons [79].

Treatment

The simplest method of removing the excess iron is by venesection and is continued till the serum iron is normal and the transferrin saturation less than 50%. If the iron stores are normal, further venesection will be necessary to maintain the transferrin saturation at 10% or lower. If untreated it can lead to a number of complications such as cirrhosis, cardiomyopathy and diabetes.

Impact

The various changes that occur in the liver with ageing could affect the clinical characteristics and outcomes in patients with some liver disease [80]

compared to the younger patient [81]. Viral infections are the commonest cause of chronic liver disease. Alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, drug-induced hepatitis and metabolic diseases such as alpha-antitrypsin deficiency are the other causes. With chronic liver disease (CLD), health-related quality of life is an important outcome measure [82, 83]. Health-related quality of life (HR-QoL) may be reduced by the chronic liver disease, and the impact did not differ markedly by type of disease but rather by older age and severity [84]. Others have found that the aetiology of liver cirrhosis with hepatocellular or cholestatic aetiologies has higher HR-QoL than those with alcohol or viral aetiologies [85]. Patients with cirrhosis of the liver show signs of psychological distress and depression in relation to severity of the disease [86]. Patients with cirrhosis especially those with age-related morbidities go through several possible incapacitating complications which can impair activities of daily living [87].

Compared to non-cirrhotics the healthcare services are double in those with cirrhosis, and this is largely due to physician's visits, nursing home stays, hospitalisation and disability [88]. It has been estimated that 5.5 million Americans have chronic liver disease and is costing $1.6 billion annually in healthcare costs and loss of work days [89]. Older Americans with cirrhosis have higher rates of disability, healthcare utilisation and need for informal caregivers, and it has been estimated that the annual cost is $4,700.00 per person [87].

A proportion of the patients with chronic infection with hepatitis C virus (HCV) will develop cirrhosis and associate with impairments in HR-QoL [90]. Several health utility measures such as SF-6D and Health Utility Index have shown that HCV patients have significant poorer health than HBV patients [91]. In hepatitis C chronic liver disease, the HR-QoL has been associated with disease severity, depression, anxiety, fatigue and cramps, among others [82]. Other studies have shown that underlying co-morbidities, marital status and income had a greater impact on QoL depending on the disease stage [90]. CLD resulting from hepatitis C has a negative impact upon QoL so does hepatitis C cancer [92]. In NAFLD there is increased risk of developing type 1 diabetes, cardiovascular diseases, common cancers with considerable mortality, progression to decompensated cirrhosis and liver cancer [93] (Boxes 3 and 4).

Box 4 Key Points: Chronic Liver Disease

Alcoholic hepatitis is a syndrome with a wide spectrum of severity, and the presenting symptoms may vary. In the more severe specific symptoms may include deep jaundice, prolonged prothrombin time, encephalopathy and liver failure.

The diagnosis of alcoholic hepatitis is based on a thorough history, physical examination and laboratory tests.

Sometimes liver biopsy may be necessary to secure the diagnosis.

About 10–15% of patients with NAFLD develop true NASH, and only around 20–30% of them develop progressive fibrosis in 32% and cirrhosis in 20%, and death occurs in 12% in 10 years [28].

Liver biopsy is recommended for a firm diagnosis of autoimmune hepatitis [48].

The drug-induced injury may be hepatocellular with elevations of aminotransferases as predominant symptoms or cholestatic injury with elevated alkaline phosphatase [56, 57] with or without hyperbilirubinaemia, or mixed [56].

The diagnosis of primary biliary cirrhosis is based on sustained elevation of serum markers of cholestasis, namely, alkaline phosphatase, gamma G transaminase and the anti-mitochondrial antibodies (AMA).

The most common genetic defect in hereditary haemochromatosis is the homozygosity for the C282Y causing excessive iron absorption and overload and was found in 52–100% on clinically diagnosed probands [72].

- Heterozygotes for either C282Y or H63D may not manifest clinical iron

(*continued*)

Box 4 Key Points: Chronic Liver Disease (continued)

overload, and heterozygosity for C282Y/H63D results in clinically evident iron overload [73].

- It is only in the fifth or sixth decade that the manifestations of organ damage appear.
- Excessive iron binding saturation of transferrin exceeding the normal value of 50%, serum ferritin in excess of 1,000 ngm/ml and elevation of serum liver enzymes are found in HH.
- The demonstration of the iron content in the liver by liver biopsy is the gold standard which confirms the diagnosis, for detection of cirrhosis, to determine prognosis and the need to screen for hepatocellular carcinoma.
- First-degree relatives of the individual with the condition should be screened by iron studies and genetic testing.
- The simplest method of removing the excess iron is by venesection.

Multiple Choice Questions

1. The following clinical manifestations of haemochromatosis are true, except:
   A. Symptoms may be non-specific: fatigue, malaise, joint pains and increased pigmentation.
   B. May present with cardiac symptoms, for example, atrial fibrillation.
   C. May complain of erectile dysfunction.
   D. Pigmentation marked over pressure points, palmar creases, skinfolds and mucous membranes of the lips, mouth, rectum and vagina.
2. The following investigation findings relating to the diagnosis of haemochromatosis are true except:
   A. Fasting transferrin saturation exceeds the normal value of 50%.
   B. Random sugar abnormal.
   C. Serum ferritin is in excess of 1,000 ngm/ml.
   D. Cortisol levels are low.
3. The following relating to genotyping in haemochromatosis are true except:
   A. Homozygosity for C282Y causes excessive iron absorption and overload.
   B. Heterozygous for C282Y and H63D may not manifest iron overload.
   C. Heterozygosity for C282Y/H63D may not manifest iron overload.
   D. First-degree relatives of the individual with HH should be screened by transferrin saturation and genetic testing.

MCQ Answers

1 = D; 2 = D; 3 = C

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Hepatocellular Carcinoma

23

Contents

Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. Patients with hepatocellular carcinoma are at high risk of developing HCC. Risk factors for developing HCC include dietary aflatoxin (AFB1) ingestion, chronic alcoholism, chronic hepatitis virus (HBV, HCV) infections and hereditary conditions such as hereditary hemochromatosis. Hepatic carcinogenesis is a complex process and is associated with genetic and epigenetic changes, and different genes have been implicated in the pathogenesis.

Keywords

Hepatocellular carcinoma · Aflatoxin · Hereditary hemochromatosis · Cirrhosis of the liver

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide [1, 2, 3] and is the fifth common cancer [4]. Its incidence is rising worldwide [5] with an incidence of one million cases a year [2]. It has doubled over the past three decades in the United States [6]. There is a geographical variation [1] and is highly prevalent in the Asia-Pacific region and Africa [6, 7]. White Americans are two to three times less affected than African Americans who are in turn two to three times less affected than Asians and Pacific Islanders [151].

Patients with cirrhosis of the liver are at high risk of developing HCC [8], and it has been found that 70–90% of patients with HCC have chronic liver disease and cirrhosis [8]. Risk factors for developing HCC include dietary aflatoxin (AFB1)

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_24

ingestion, chronic alcoholism, chronic hepatitis virus (HBV, HCV) infections [9–11] and hereditary conditions such as hereditary hemochromatosis and alpha1-antitrypsin deficiency [2] and genetic alterations [8]. Furthermore, the risk of developing HCC is known to be age dependent [12, 13], and in the United States, the incidence of HCC peaks above the age of 70 years [14].

Hepatic carcinogenesis is a complex process and is associated with genetic and epigenetic changes [2, 9], and different genes have been implicated [1] in the pathogenesis. A number of mechanisms have been recognised that speed up HCC which include telomere dysfunction and alterations that stimulate cell proliferation [15]. In cirrhosis, there is decrease in hepatocyte proliferation and activation of pro-inflammatory pathways [8] which may affect hepatocyte proliferation. Oncogenic pathways are activated [153]. The direct oncogenic effect of HBV is well known, and HBV is able to integrate its DNA into the host cells [10] which may act as insertional mutagens [1] causing genomic instability and chromosomal derangement [16]. The mechanism in the case of hepatitis C virus is less clear [1, 10]. The role of suppressor genes such as retinoblastoma (RB) and p53 has been recorded [1], and RB1 and p53 and Wnt pathways are commonly affected in HCCs of different aetiologies [9]. Alterations in the RB1 pathway are seen in hepatitis virus infection-associated HCC, and alterations in the P53 with AFB1 exposure and alterations of both RB1 and p53 are seen in alcoholism-associated HCCs [9].

Clinical Expression

The clinical characteristics of HCC in elderly patients may differ in several aspects from that in younger patients. In the elderly group, there are significantly more women [17], the occurrence of normal liver in patients with HCC is said to be higher compared to the younger [162, 163, 164] and HCC appears to develop even without fibrosis in the elderly. [17]. The number of HCC nodules has been reported to be less than in younger patients [18–20].

Diagnosis

The determination of alpha-fetoprotein (AFP) alone is not adequate enough for effectual surveillance [21, 22] and for diagnosis although it has the highest sensitivity followed by PIVKA-II and ALP-3 [7]. The specificity is the reverse in that order [7]. Ultrasound is less effective for detecting early HCC with a sensitivity of 63% [21]. Biomarkers are required to complement ultrasound in the detection of early HCC, but neither AFP nor des-gamma-carboxy prothrombin (DCP) is adequate [22]. Currently, the screening strategy is abdominal ultrasound examination every 6 months [23, 24] together with determination of AFP levels in patients with cirrhosis for the detection of early HCC [24]. To characterise hepatic tumours, sonazoid-enhanced ultrasound is very useful [7], and Gd-EOB-DTPA magnetic resonance is a sensitive tool in the differentiation of early HCC from dysplastic nodules [7].

Management

The Barcelona Clinic Liver Cancer (BCLC) staging system has come to be widely accepted as a staging system in clinical practice [25], and HCC patients can be categorised into different prognostic subgroups [26]. According to the BCLC staging, the curative treatment group included early stage HCC (BCLC-A), and the non-curative consisted of intermediate and advanced stages of HCC (BCLC-B, BCLC-C) [27]. Liver function and tumour stage rather than age influence the outcome of HCC in elderly patients [28]. The Child-Pugh classification of cirrhosis of the liver is based on five parameters, namely, ascites, bilirubin, albumin and prothrombin/INR levels and encephalopathy and categorised as compensated disease (A), disease with significant functional impairment (B) and decompensated disease (C) [29, 30]. Transarterial chemoembolization (TACE) is the mainstay in the treatment for intermediate stage HCC with Child-Pugh A cirrhosis [27]. Curative therapies include surgical resection, radiofrequency ablation and liver transplantation and are reserved for early stage and with

good prognosis [26, 31]. Palliative care is the best option for those with distant metastases [26]. For patients with advanced tumours (locally advanced but unresectable and those with metastasis) not suitable for surgical therapies, sorafenib (Nexavar), a multikinase inhibitor, has been shown to prolong median overall survival in randomised control trials [27] and is one of the treatment options [27, 28, 31].

Impact

In elderly patients with hepatocellular carcinoma, optimal treatment strategy may be difficult to detail because of the presence of comorbidities [32]. Another limitation is 25–50% of people 85 years and over are frail [32], and frailty is increased with cancer and treatment [33]. The risk of liver cancer is considered to be age dependent though the influence of age in the prognosis is debatable [34]. Younger patients with liver cancer have a higher 5-year liver cancer-specific survival in spite of the poorer biological behaviour of the carcinoma compared to the elderly patients [34] (Box 1).

Box 1 Key Points: Hepatocellular Carcinoma

- Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide [1–3].
- There is a geographical variation [1] and is highly prevalent in the Asia-Pacific region and Africa [6, 7].
- Hepatic carcinogenesis is a complex process and is associated with genetic and epigenetic changes [2, 9].
- A number of mechanisms have been recognised that speed up HCC which include telomere dysfunction and alterations that stimulate cell proliferation [15].
- Oncogenic pathways are activated [8].
- The role of suppressor genes such as retinoblastoma (RB) and p53 has been recorded [2].

Box 1 Key Points: Hepatocellular Carcinoma (continued)

The clinical characteristics of HCC in elderly patients may differ in several aspects from that in younger patients [17].

- Currently, the screening strategy is abdominal ultrasound examination every 6 months [23, 24] together with determination of AFP levels in patients with cirrhosis for the detection of early HCC [24].
- Liver function and tumour stage rather than age influence the outcome of HCC in elderly patients [28].

Multiple Choice Questions

1. The following are true of hepatocellular carcinoma (HCC), except:
   A. The clinical characteristics of HCC in elderly patients may differ in several aspects from that in younger patients.
   B. The number of HCC nodules has been reported to be more than in younger patients.
   C. Patients with cirrhosis of the liver are at high risk of developing HCC.
   D. HCC appears to develop even without fibrosis in the elderly.

MCQ Answers

1 = B

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Ascites in the Elderly

24

Contents

Abstract

The pathophysiology of ascites is complex. The complications of cirrhosis include ascites, varices, hepatic encephalopathy, hepatocellular carcinoma, hepato-pneumonic syndromes, spontaneous bacterial peritonitis and hepatorenal syndrome. The review discusses the pathophysiology of ascites and the recent advances in the clinical management.

Keywords

Ascites · Cirrhosis of the liver · Spontaneous bacterial peritonitis · Malignant ascites

Introduction

The complications of cirrhosis include ascites, varices, hepatic encephalopathy, hepatocellular carcinoma, hepato-pneumonic syndromes [1], spontaneous bacterial peritonitis and hepatorenal syndrome [2]. Ascites is the accumulation of fluid in the peritoneal cavity due to a wide range of causes. In a study of 107 patients over 5 years, 52% of the patients presented with ascites at the time of initial cancer diagnosis, 20 had cancer of the pancreas, 18 ovarian and 18 that of the colon. Cytology evaluation of the ascitic fluid was positive for tumour cells in 51%, and a high protein content was seen in 65% [3]. Approximately 10% of all ascites is malignant [4] and the remaining due to heart failure (3%), tuberculosis (2%) and pancreatitis (1%) [5]. Ascites is an important complication of cirrhosis (70%) [5] and occurs in about half the number of the patients within the 10 years of diagnosis [6].

The pathophysiology of ascites is complex, and there is more than one theory to explain the ascites formation. The first abnormality to occur in the cirrhotic patient is the increase in the portal vein pressure due to resistance of blood flow within the liver. As a result blood is shunted into the splanchnic and systemic circulation which in turn may influence renal function [7]. The arterial

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_21

blood flow and arterial pressures are decreased due to release of vasodilators with vasodilator effect on the splanchnic arterial circulation and which may act as a trigger for nitric oxide (NO), the likely vasodilator mediator [8]. Portal hypertension also plays a role in sodium retention which occurs in the setting of increased renin-angiotensin aldosterone system (RAAS) [9] and sympathetic nervous system (SNS) activity [10, 11]. The mechanism by which portal hypertension leads to activation of these systems and sodium retention is not clear [12]. There is also an overall activation of the renal prostaglandin system [10] which probably acts to maintain renal haemodynamics and glomerular filtration rate by counteracting the vasoconstricting effects of AII and noradrenaline in the renal circulation. In advanced cases there is marked vasoconstriction of the renal arteries and the opening of intra-arterial-venous shunts due to reduced renal synthesis of vasodilating prostaglandins [7] leading eventually to acute renal failure, the so-called hepatorenal syndrome [10].

The pathophysiology of malignant ascites is not clear. Mechanisms involved are increased vascular permeability, metalloproteinases that degrade the extracellular matrix [13, 14], tumour-related obstruction of lymphatic drainage and overactive renal-angiotensin-aldosterone system [14], among others. It has been surmised that the biologically active peptides produced by the tumour cells such as vascular endothelial growth factor and basic fibroblast growth factor may be the cause of the increased intraperitoneal oncotic pressure. This is the result of an increased net filtration brought about by an overall increase in the capillary membrane surface and increased capillary permeability and a consequential increase of intraperitoneal protein concentration [15]. Spontaneous bacterial peritonitis usually occurs in patients with cirrhosis of the liver and portal hypertension [6] and in ascites with high serum-ascites gradient [16] and occasionally in malignant ascites [17].

Ascites occurs in chronic liver disease, peritoneal disorders and systemic diseases (Box 1). It is a common complication of cirrhosis of the liver [6]. Peritoneal involvement due to carcinomatous peritonitis occurs in another 10%, and congestive heart failure may be ranked third. Less common hepatic causes are chronic hepatitis, alcoholic hepatitis, fulminant hepatic failure and Budd-Chiari syndrome and system diseases such as SLE, constrictive pericarditis, pancreatitis, myxoedema or infective peritonitis. Malignant ascites is seen most commonly in patients with ovarian, endometrial, breast, colon, gastric and pancreatic cancers [18].

Box 1 Causes of Ascites in the Elderly

i. Cirrhosis of liver
ii. Malignant ascites
Ovarian, endometrial, breast, gastric, colon and pancreas
iii. Non-hepatic
Congestive heart failure
Severe hypoalbuminaemia
Nephrotic syndrome

Symptomatology

The patient may be asymptomatic with small amount of fluid; with moderate amounts, there may be weight gain and increase in the girth of the abdomen. In increased amounts the abdominal wall will be tense with flattening of the umbilicus. Infection of the ascitic fluid without any apparent cause is called spontaneous bacterial peritonitis. It is common in cirrhotic ascites and in alcoholics and is often the cause for unexplained clinical deterioration. It is usually associated with lethargy, fever, encephalopathy, worsening hepatic failure and abdominal tenderness.

Diagnosis

History, physical examination, diagnostic paracentesis, cell count, cytology, protein content, lactic acid dehydrogenase and culture will usually provide the diagnosis. Physical examination findings parallel the amount of fluid. In significant amounts there will be abdominal fullness with fullness in the flanks

and shifting dullness. If physical examination is not definite, ultrasonography may be used.

Diagnostic paracentesis should be performed if the cause is not known, is newly diagnosed or if spontaneous bacterial peritonitis is suspected. The ascites may be differentiated by the nature of the fluid. It is more useful to calculate the serum albumin gradient (serum albumin-ascites albumin) (SAAG) rather than differentiating into 'transudate' and 'exudate' [4, 19, 20]. The SAAG is based on the concept that if there is high portal pressure, there will also be a high oncotic gradient with albumin contributing to the major component of the serum proteins. Evaluating the SAAG is a better way in the differential diagnosis distinguishing [20] and separating the causes [21]. An elevated SAAG correlates with portal hypertension [19]. Low gradient ascites is associated with tuberculous peritonitis, malignancy, pancreatic, renal and biliary-induced ascites [22]. A high gradient ascites occurs with uncomplicated cirrhosis of the liver, fulminant hepatic failure and extensive liver metastases [23, 24]. See Box 2.

Box 2 Classification of Ascites Based on SAAG

High gradient >1.1 g/dL	Low gradient <1.1 g/dL
Cirrhosis	Pancreatic induced
Carcinomatosis	Malignancy
Cardiac	Tuberculosis
Massive liver metastases	Nephrotic syndrome
Other hepatic causes*	Connective tissue
Myxoedema	Disorders

Information sources: Mansour-Ghanaei et al. [22]; Chung and Podolsky [23]; Glickwan [24]

Prognosis and Treatment

The occurrence of ascites in the patient with cirrhosis is a prognostic sign with 85% and 56% surviving for 1 year and 5 years, respectively [6]. Dietary sodium restriction (20–40 mEq/day) and bed rest are the judicious treatment for ascites due to portal hypertension [10]. If rigid sodium restriction and conscientious adherence to a diet are unsuccessful or if the ascites is massive, intervention with diuretics may be necessary. Spironolactone is usually effective (50–200 mg bid) and a loop diuretic such as frusemide added (20–100 mg bid) if spironolactone alone fails. The combined provides optimal diuresis with low risk of potassium abnormality. A weight loss of 0.5 kg/day is aimed at or diuresis of less than 900 ml per day. More aggressive diuresis will be at the expense of the plasma compartment and volume contraction resulting in renal failure or electrolyte imbalance and precipitate portosystemic encephalopathy.

Because of the possible risk of renal failure, electrolyte imbalance and encephalopathy abdominal paracentesis had not been favoured. More recently abdominal paracentesis has been evaluated by several investigators who have suggested that in cases of refractory ascites either repeated removal (about 4 L/day is safe) or total removal will have to be associated with concomitant intravenous infusion of albumin of ascitic fluid removed [6]. Transjugular intrahepatic portosystemic shunt (TIPS) was devised to treat complications of portal hypertension. According to Boyer and Haskel Ziv [25], TIPS should not be considered as primary therapy for any complication of portal hypertension except for bleeding gastric or ectopic varices. It can be associated with a number of complications.

Abdominal paracentesis is done if the ascites is causing respiratory difficulty or pain or as treatment for chronic ascites. It is absolutely contraindicated when there is severe uncorrectable disorder of blood coagulation, infected abdominal wall and intestinal obstruction. Haemorrhage and prolonged leakage of the ascitic fluid are a common complication. If spontaneous bacterial peritonitis is suspected, an antibiotic like cefotaxime 2 g iv q4 to 8 hourly can be given (pending culture results and Gram stain) for at least 5 days. About 75% of the patients with spontaneous bacterial peritonitis have a recurrence within a year, and a prophylactic antibiotic will be needed [6]. An antibiotic like norfloxacin 400 mg once a day has been recommended [16].

Impact

Ascites is an important complication of cirrhosis (70%) [6]. About half the number of patients with cirrhosis of the liver die within 2 years [26]. It is believed that there will be a huge increase in burden of liver disease in the coming years due to the increasing frequency of alcoholic and non-alcoholic fatty liver disease [27] with an increase in complications of cirrhosis which not only impair quality of life but also decrease survival [1]. The survival rates are worse in patients with cirrhosis in the presence of ascites [28] (Box 3).

Box 3 Key Points: Ascites in the Elderly

Ascites is an important complication of cirrhosis (70%) [5] and occurs in about half the number of the patients within the 10 years of diagnosis [6].

Malignant ascites is seen most commonly in patients with ovarian, endometrial, breast, colon, gastric and pancreatic cancers [18].

It is more useful to calculate the serum albumin gradient (serum albumin-ascites albumin) (SAAG) rather than differentiating into 'transudate' and 'exudate' [5, 19, 20].

High gradient ascites is due to cirrhosis of the liver, massive liver metastases and fulminant hepatic failure [23, 24]).

Low gradient ascites includes tuberculosis, nephrotic syndrome, pancreatic, biliary, bacterial-induced and peritoneal carcinomatosis [22].

The occurrence of ascites in the patient with cirrhosis is a prognostic sign with 85% and 56% surviving for 1 year and 5 years, respectively [6].

Dietary sodium restriction (20–40 mEq/day) and bed rest; spironolactone is usually effective (50–200 mg bid); a weight loss of 0.5 kg/day is aimed at or diuresis of less than 900 ml per day.

More recently abdominal paracentesis in cases of refractory ascites either repeated

Box 3 Key Points: Ascites in the Elderly (continued)

removal (about 4 L/day is safe) or total removal will have to be associated with concomitant intravenous infusion of albumin of ascitic fluid removed [6].

If spontaneous bacterial peritonitis is suspected, an antibiotic like cefotaxime 2 g iv q4 to 8 hourly can be given (pending culture results and Gram stain) for at least 5 days.

Multiple Choice Questions

1. The following in relation to ascites are true, except:

A. Eighty percent of the ascites in cirrhosis of liver is due to portal hypertension.
B. Spontaneous bacterial peritonitis usually occurs in cirrhosis of the liver with portal hypertension and ascites with high serum-ascites gradient.
C. Seventy-five percent of spontaneous bacterial peritonitis will recur within the year, but prophylactic antibiotic is not needed.
D. Total removal of ascitic fluid has to be associated with concomitant intravenous infusion of albumin of ascitic fluid removed.

MCQ Answers

1 = C

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Part V

Blood Disorders in the Elderly

Part V provides an overview of the blood disorders in the elderly which includes the anemias and the hematological neoplasms. This review discusses the pathogenesis of the anemias, their clinical manifestations and presents an algorithm for their evaluation and management. The review will further contribute an update on the recent changes to the terminology and classification and highlight the improvement that have occurred in clinical care. Myeloproliferative neoplasms (MPNs) formerly known as chronic myeloproliferative disorders are clonal hemopoietic stem cell disorders characterized by excessive production of mature blood cells. The World Health Organization system currently recognizes eight types of MPN: chronic myelogenous leukemia, chronic neutrophilic leukemia, polycythemia vera, primary myelofibrosis, essential thrombocythemia, chronic eosinophilc leukemia, masocytosis, and myeloproliferative neoplasms, unclassifiable. The classic MPNs are polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF) (Phi-negative), and chronic myelogenous leukemia (CML). The central role of protein tyrosine kinases in their pathogenesis has been identified, and the new classification system embraces mutations discovered in the JA2 and MPL genes. CML and other MPNs are classified on the basis of the presence or absence of the BCR-ABL1 fusion gene which is the hallmark of CML. The BCL-ABL1-negative MPN include PV, ET, and PMF, and they are associated with three types of molecular markers namely activating mutations in the JAK2 gene, activating mutations in the MPL gene, and alterations of CALR the gene coding calreticulin (CALR) detected in ET and PMF. A significant proportion of patients with PV, ET, and PMF have been identified with JA2 tyrosine kinase (JAK2V617F). According to the Polycythemia Vera Study Group (PVSG), the majority of PV patients are JAK2 V617F positive on the polymerase chain reaction (PCR) test whereas only about 50% of the ET and PMF patients are positive.

The Anaemias

25

Contents

Abstract

Haemopoietic stem cells (HSCs) are responsible for the production and replenishment of major lineages of blood and immune cells throughout life. There is an age-related decline in haemoglobin from age 70 to 88 among healthy men and less marked in women. This review discusses the pathogenesis of the anaemias and their clinical manifestations and presents an algorithm for their evaluation and management. Anaemias may result from blood loss, inadequate red cell production and excessive red cell destruction. The review provides an overview of the common types of anaemias in the elderly, the iron deficiency anaemia, anaemia of chronic disease and vitamin B12 and folic acid deficiencies and their mechanisms and clinical management. An elderly presenting with iron deficiency is almost exclusively due to blood loss from the gastrointestinal tract. A wide variety of iron preparations are available. Parenteral iron therapy is safe and effective in iron deficiency anaemia. Anaemia of chronic disease (ACD) also referred to as anaemia of chronic inflammation (ACI) is the most common form of

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_29

anaemia in the elderly, and several diseases (acute and chronic infections, inflammatory disorders and neoplasms) are associated with ACD. Many old people suffer from a deficiency of vitamin B_{12} (cobalamin). Many neurological and psychiatric symptoms may occur, alone or in association with the haematological abnormalities, and may be present in the absence of anaemia.

Keywords
Haemopoietic stem cells · Iron deficiency anaemia · Anaemia of chronic disease · Vitamin B12 deficiency

Introduction

Haemopoietic stem cells (HSCs) are responsible for the production and replenishment of major lineages of blood and immune cells [1] throughout life. HSCs reside in the bone marrow in a physical niche with a specific microenvironment [2] and which control their destiny. The aging microenvironment is associated with stem cell intrinsic and extrinsic changes which could contribute to the ageing of the haemopoietic system [3]. The effect of age on the regenerative capacity is unclear [4, 5]. Dysregulation of mechanisms controlling haematopoiesis results in age-associated pathophysiological changes such as diminished adaptive immune competence, greater propensity to anaemia and a skewing toward a myeloid-biased disorder [3, 6–8]. There is an age-related decline in haemoglobin from age 70 to 88 among healthy men and less marked in women [9]. Even though the number of stem cells decreases with age, the marrow in older people can repopulate the blood system after serial transplantations [10], and marrow failure in the elderly is rare, implying that stem cell exhaustion does not accompany normal aging [11].

Anaemias may result from blood loss, inadequate red cell production and excessive red cell destruction. Deficient red cell production could result from defects in stem cell proliferation or differentiation, haemoglobin synthesis, DNA synthesis or a combination of these. Excessive destruction could result from abnormalities in the red cell membrane (membranopathies), enzyme deficiencies (enzymopathies) or abnormal haemoglobins (haemoglobinopathies) (Table 1).

Anaemias can be classified according to their pathogenesis, but a more useful way diagnostically would be to base it on the size of the red cells, as measured by the mean cell volume

Table. 1 Anaemias classified as to cause and morphology

Cause	Morphology
Blood loss	
Acute	Normocytic normochromic
Chronic	Microcytic hypochromic
Deficient erythropoiesis	
Iron deficiency	Microcytic hypochromic
Protein depletion, thyroid pituitary, kidney disease	Normocytic normochromic
Vitamin B12 deficiency	
Folate deficiency vitamin C	Macrocytic
Excessive haemolysis	
Extrinsic RBC deficits	
Haemolytic anaemias (acquired) (*iso*-immune, autoimmune)	Normocytic normochromic
Intrinsic RBC deficits	
Membranopathies (HS,HE)	Spheroidal microcytic elliptocytic
Enzymopathies (G6PD, etc.)	Blister or bite cells
Haemoglobinopathies synthesis (thalassaemias) (sickle cell, Hb C, etc.)	Microcytic hypochromic chemical structure, some sickle cell, target cells, etc.

(MCV). The method classifies the anaemias into three categories, normocytic, microcytic and macrocytic. Some of the anaemias may fall into more than one category.

Clinical Manifestations

Iron Deficiency Anaemia

An elderly presenting with iron deficiency is almost exclusively due to blood loss from the gastrointestinal tract. The causes of blood loss in the elderly include neoplasms, drugs such as aspirin and angiodysplasia of the large bowel. Bleeding from the upper gastrointestinal tract due to gastric cancer, peptic ulcers, gastritis and oesophagitis accounts for 20–40% of cases [12, 13]; colon cancer, angiodysplasia or colitis accounts for 10–30% of cases, and 1–15% of patients may have bleeding lesions in both the upper and lower gastrointestinal tract and the source of the bleed is not found in 10–40% of patients [12, 13]. In iron deficiency anaemia, the MCV is usually reduced and the peripheral blood smears show microcytic hypochromic cells. Chronic bleeding also results in elevated platelet count. A transferrin saturation of $<16\%$ may indicate iron deficiency, but this may not always be useful as both serum iron and total iron binding capacity decrease in chronic disease.

Treatment

A wide variety of iron preparations are available. They include ferrous salts such as ferrous fumarate, ferrous sulphate, ferrous gluconate and ferrous succinate or as saccharated iron [14]. The recommended daily oral dose is 300 mg of ferrous sulphate, to be taken 1–2 h before meals if tolerated or otherwise after food to lessen gastrointestinal side effects such as epigastric discomfort, nausea or vomiting. The increase in haemoglobin concentration may take several weeks, e.g. 2 g/dl in 3 weeks, whilst correction of the anaemia and replenishment of iron stores may take several months.

Parenteral iron therapy is safe and effective in iron deficiency anaemia including patients with cancer [15], in severe iron deficiency in uraemic haemodialysis patients receiving recombinant human erythropoiesis (rHuEPO) [16], in patients who are intolerant to oral iron or have gastrointestinal dysfunction hindering adequate intake of oral iron and in surgical patients refusing blood transfusion [17]. The available parenteral therapy includes iron dextran, iron gluconate and iron sucrose. Sodium ferric gluconate complex was shown to be effective and safe in patients with severe iron-deficient and anaemic haemodialysis patients on rHuEPO [16]. Adverse events were insignificant and were not related to the drug therapy [16]. A number of side effects have been described with parenteral iron dextran, and in the short term such anaphylaxis, arthralgia, lymphadenopathy and pruritis amongst others and in the long term complications for both IV and IM are iron overload [17].

Anaemia of Chronic Disease (ACD)

Anaemia of chronic disease (ACD) is also referred to as anaemia of chronic inflammation (ACI) and is the most common form of anaemia in the elderly, and several diseases (acute and chronic infections, inflammatory disorders and neoplasms) are associated with ACD. In ACD the anaemia is due to the inability to reutilise, i.e. recycle the iron that is derived from breakdown of the senescent red cells. In ACD the iron is retained in the reticuloendothelial cells thus making it unavailable for haemoglobin synthesis. There is also a slightly shortened survival of red blood cells. Furthermore it had been postulated that there is an age-dependent increase in the production of the proinflammatory cytokine IL-6 [18], and the cytokine dysregulation may be involved in the pathogenesis, specifically by influencing both erythropoietin production and erythropoietin responsiveness. The anaemia may be microcytic but is usually normocytic.

Anaemia in the elderly is more usually of multifactorial aetiology, due to concomitant problems. For example, an elderly patient with rheumatoid

arthritis taking NSAIDS or aspirin has anaemia of chronic disease and anaemia due to blood loss. The anaemia of ACD is usually mild to moderate with a haemoglobin concentration not below 10 g/dl. When ACD is associated with a haemoglobin below 10 g/dl, the possibility of multifactorial aetiology should be considered.

Differentiating between iron deficiency and anaemia of chronic disease may be difficult. The serum iron levels are low in both. Microcytes may be present in both. In iron deficiency anaemia, the TIBC is high, but in ACD, it is usually below normal. In about 70% of patients, serum ferritin level helps to differentiate iron deficiency anaemia from ACD. In some patients with ACD (liver injury, infection, inflammation, malignancy), ferritin could be an active-phase reactant raising the serum ferritin to normal levels even in the presence of iron deficiency. Serum ferritin (SF) concentrations tend to rise after the age of 60 due to either increased iron stores or effect of increasing development of inflammatory disease [19]. Normal or high levels do not rule out iron deficiency [20]. Some authors have found the cut-off level for SF at 30 ug/L had a sensitivity of 48% and specificity of 100%, whilst a cut-off at 65 ug/L increased the sensitivity to diagnose iron deficiency to 80% and the specificity to 99% [21]. Age-specific criteria should be applied to this population as the sensitivity of SF in detecting iron deficiency is reduced (due to elevation of SF during inflammation), and haemoglobin levels in the elderly men may be lower than in 18–44-year-old males. However, serum transferrin saturation is found to be the best test for distinguishing those who are iron deficient and those who are not [20]. When both iron deficiency and ACD are present together, a bone marrow aspiration is the only way to identify the true cause of the anaemia [22].

Treatment

The treatment of ACD is primarily the treatment of the underlying disease. Recombinant erythropoietin therapy frequently corrects the anaemia but is expensive, and blood transfusions are rarely required.

Vitamin B12 Deficiency

Many old people suffer from a deficiency of Vitamin B12 (cobalamin). About 3–40% of the general population [23–25] and 15–25% of the patients in the community, hospital and nursing homes [24, 26] are cobalamin deficient. A Swedish study found 11% of men and women 75 years or older to be cobalamin deficient [27], and in another study, 40.5% of the elderly people were noted to have vitamin B12 deficiency [28].

The clinical presentation may vary. The patient may remain asymptomatic until the haemoglobin concentration is very low. Leucopenia and/or thrombocytopenia may be severe, and as a result of ineffective erythropoiesis and intramedullary haemolysis, the serum bilirubin may be elevated with clinical jaundice, and lactic dehydrogenase too is elevated. In the mouth there may be mucosal changes giving rise to 'beefy red tongue'. Many neurological and psychiatric symptoms may occur, alone or in association with the haematological abnormalities, and may be present in the absence of anaemia. Vitamin B12 deficiency patients may develop neuropsychiatric damage and show signs of disorientation and confusion long before the megaloblastic anaemia becomes evident [29]. The neurological symptoms include subacute combined degeneration, ataxia and peripheral sensory or motor neuropathy and mononeuropathy (optic or olfactory atrophy, perversions of taste and smell, central visual scotomas [30]. Neuropsychiatric symptoms are confusion, irritability, dementia, delirium ('megaloblastic madness') agitation and rarely coma [30].

Diagnosis

Diagnostic tests may be divided into (1) the detection of B12 deficiency and (2) as to its cause.

Screening

Measurement of B12 levels is inexpensive and readily available. False positives (low levels) occur in folate deficiency, multiple myeloma,

pregnancy and excessive intake of vitamin C, and false negatives occur in true deficiency, active liver disease, lymphoma, autoimmune disease and myeloproliferative disorders [30].

B12 deficiency results in methyl malonic aciduria and measurement of serum methyl malonic acid (MMA) in the serum or urine is a very sensitive test for B12 deficiency [31]. Elevated levels of MMA were found in 23% of healthy elderly people and 39% in elderly hospitalised patients [32]. Vitamin B12 deficiency also leads to accumulation of homocysteine in the blood [21]. When the results are at or near the lower limit of the normal range, serum or urine MMA and homocysteine levels should be measured [31, 33] if available. Blood counts, peripheral smear (Fig. 1) and bone marrow examination should be done.

The role of Schilling test in routine evaluation of vitamin B12 deficiency is unclear. It is not a test to identify B12 deficiency but rather to identify why the patient became B12 deficient. It indirectly measures the absorption of orally administered radiolabelled vitamin B12 by measuring the fraction excreted in the urine. The results can differentiate between lack of intrinsic factor (pernicious anaemia) and malabsorption, chronic pancreatitis and small bowel intestinal bacterial over growth (SIBO). However, because of the need for accurate 24 h urine collection, it is of limited value especially in renal failure which is common among the elderly [33] (Fig. 2). The algorithm presents a diagnostic approach to patients presenting with, or found to have, an anaemia.

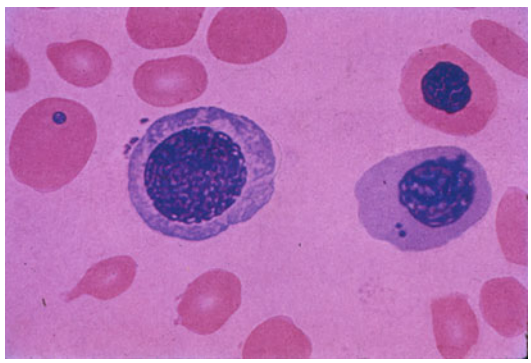


Fig. 1 Blood smear. Pernicious anaemia: showing basophilic, polychromatic and orthochromic megaloblasts. Note nucleocytoplasmic dissociation. Also seen are macrocytes with Howell Jolly body and poikilocytosis (Reproduced, with kind permission, from Norvatis Company Archives,"Sandoz Atlas of Haematology" FA Sandoz,1973)

Treatment

In the elderly B12 deficiency may be prevented by giving 25–1,000 ug daily of cyanocobalamin orally. In patients with a proven deficiency state, B12 1,000 ug IM is given two to four times a week until the haematological abnormalities are corrected (this usually takes about 6 weeks) and then continued once a month. Should there be any neurological symptoms, B12 is given twice a month for 6 months and continued with monthly injections. Neural improvement may take up to 18 months. If vitamin B12 deficiency due to megaloblastic anaemia is not treated, it could lead to irreversible neurological damage.

Folic Acid Deficiency

Folic acid (folate) deficiency is frequently found with excessive alcohol consumption and protein energy malnutrition. Anaemia occurs within 3–4 months of the deficiency. Alcohol and drugs (methotrexate, trimethoprim, triamterene) interfere with folate absorption. Pregnancy, thyrotoxicosis, malignancy, haemolytic anaemia and psoriasis may increase the folate requirements and increase the vulnerability to folic acid deficiency. Impaired absorption is seen in ileal disease, tropical and nontropical sprue and phenytoin use.

Pure folate deficiency may result in neurological abnormalities which are indistinguishable from that of B12 deficiency. The haematological profile is similar to that described for vitamin B12 deficiency. Diagnostic features include a low serum folate level and low red cell folate concentration. The former is less expensive [34]. As a functional marker of deficiency, neither red cell nor serum folate was superior although serum folate showed a higher correlation with

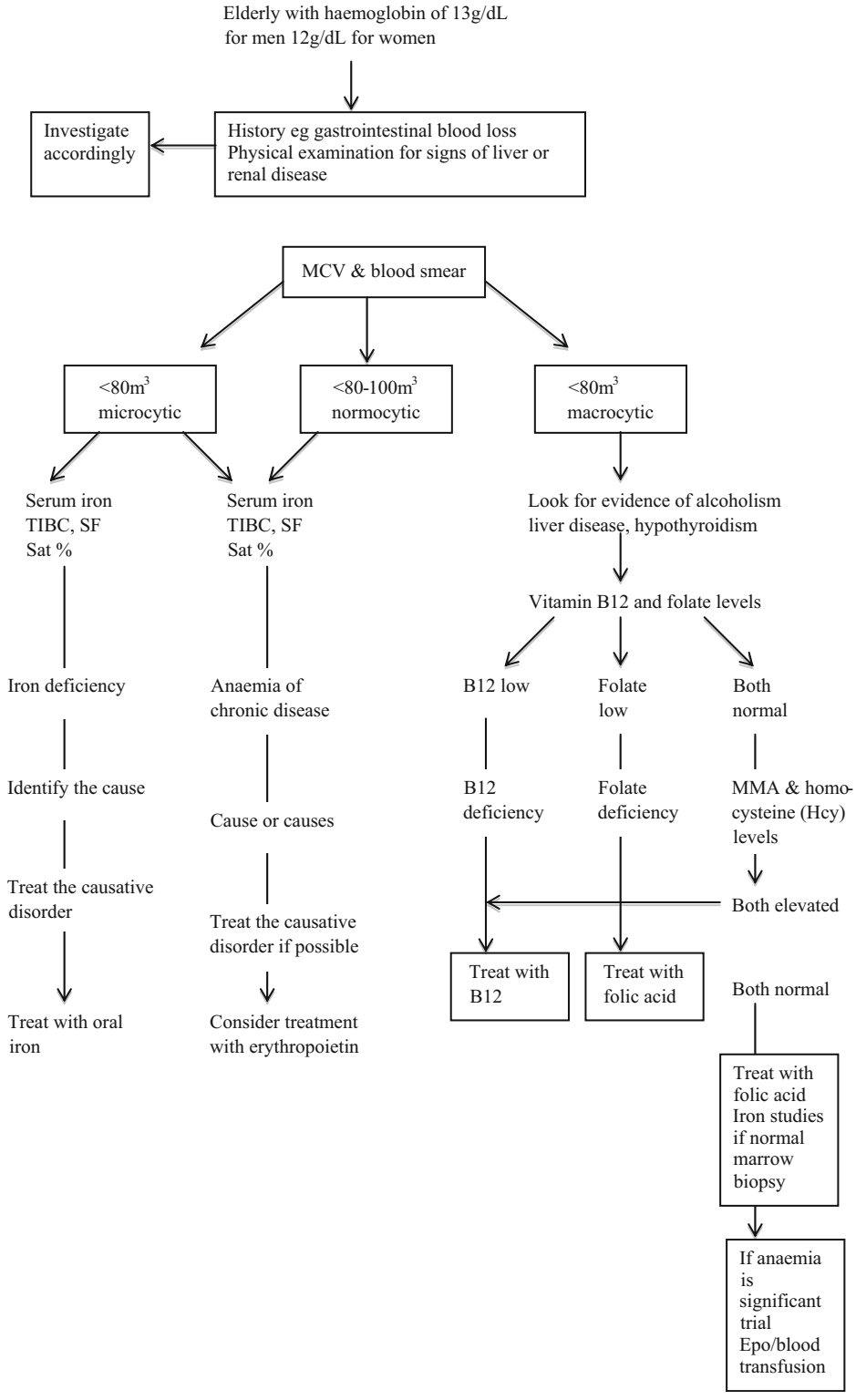


Fig. 2 Suggests an algorithm for the diagnosis of the anaemias and management

homocysteine [35]. The homocysteine (Hcy) level is elevated [36] which is associated with premature atherosclerotic disease and a heightened risk for venous thrombosis. Assay of holotranscobalamin (holoTC), the bioavailable form of vitamin B12, is not routinely available and is expensive [36].

Treatment

The normal requirement is about 50 ug/day of folate and in pregnancy and childhood two to three times more. Folate can be administered orally 1–2 mg daily. Four to 5 weeks of therapy usually reverses the anaemia as well as replenishes the body stores.

Impact

Anaemia is common in the elderly increasing with age [37–40] and a high prevalence in the last decades of life [41]. Anaemia of any degree contributes significantly to morbidity and mortality [20, 39]. It is an important predictor of negative consequences in community-dwelling and institutionalised older adults [42] and negatively impact QoL [43]. Several studies have detailed about strong associations of anaemia with major adverse functional outcomes in the elderly. It is associated in older adults with decreased cognitive [44, 45] and functional abilities, frailty, disability [44], increased risk of falls, fractures [46] and infections [47]. It has significant implications in both QoL and survival [47]. Anaemia incidence is increased in frail elderly and is a significant factor for the development of frailty-related problems [48]. Community-dwelling subjects, 85 years with anaema, had a higher 5-year mortality compared with subjects with normal haemoglobin [37]. Older individuals with anaemia including mild anaemia or even low normal level have shown lower muscle strength, physical performance and poor mobility [39, 49] with increased mortality [37, 50] and requiring increased allocation of health-care expenditure [38, 43] As a co-morbid condition, anaemia can aggravate or complicate other health conditions [38] such as diabetes, hypertension, renal disease and other age-related conditions [42]. In a report from Italy, adults aged 65–84 were at risk of hospitalisation and death by anaemia, and over a period of 3–3.5-year follow-up, hospitalisation risk increased by 32% and a twofold increase in mortality risk with older adults with mild anaemia compared to those who were not anaemic [51] (Box 1).

Box 1 Key Points: Anaemias

Bleeding from the upper gastrointestinal tract due to gastric cancer, peptic ulcers, gastritis and oesophagitis accounts for 20–40% of cases [18, 19]; colon cancer, angiodysplasia or colitis accounts for 10–30% of cases, and 1–15% of patients may have bleeding lesions in both the upper and lower gastrointestinal tract, and the source of the bleed is not found in 10–40% of patients [12, 13].

An elderly presenting with iron deficiency is almost exclusively due to blood loss from the gastrointestinal tract.

When both iron deficiency and ACD are present together, a bone marrow aspiration is the only way to identify the true cause of the anaemia [22].

Many old people suffer from a deficiency of Vitamin B12 (cobalamin) [23, 25].

Vitamin B12 deficiency patients may develop neuropsychiatric damage and show signs of disorientation and confusion long before the megaloblastic anaemia becomes evident [29].

A lack of vitamin B12 leads to the development of megaloblastic anaemia and, if untreated, to irreversible neurological damage [21]. Neural improvement may take up to 18 months.

Vitamin B12 deficiency results in methyl malonic aciduria; measurement of serum methyl malonic acid (MMA) in the serum is a very sensitive test for vitamin B_{12} deficiency [31].

(*continued*)

Box 1 Key Points: Anaemias (continued)

As a functional marker of deficiency, neither red cell or serum folate is superior [35].

Multiple Choice Questions

1. A 72-year-old man was seen with lethargy, tiredness and shortness of breath on exertion over 2–3 months. He was otherwise well and had not noticed any change in bowel habits nor has he had any gastrointestinal bleeding. He was not on any medications such as NSAIDS or aspirin. He was on a normal diet. There was no family history of bowel cancer. Physical examination revealed pallor of the mucosal membranes, and there were no other abnormalities.

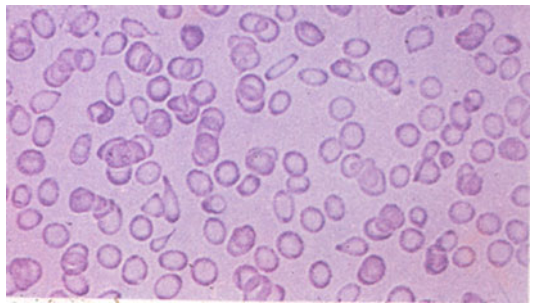
   Initial investigations: haemoglobin 70 g/L (rr 130–180 g/L)

   MCV 72 fl (rr 80–100 fl)

   WCC 12 × 109/L (rr 4.0–11.0 × 109)

   Platelet count: 450 × 109/L (rr 150–400 × 109/L)

   Blood smear as shown below



The most likely diagnosis is

   A. Thalassaemia
   B. Sideroblastic anaemia
   C. Anaemia of chronic disease
   D. Iron deficiency anaemia

   Comment: When an elderly person presents with iron deficiency anaemia, it is almost exclusively due to blood loss from the gastrointestinal tract. It is mandatory to exclude GI blood loss by endoscopy and if this is normal colonoscopy.

2. The following conditions can cause iron deficiency anaemia, except:
   A. Coeliac disease
   B. Inadequate intake
   C. Bowel cancer
   D. Thalassaemia
3. The following can cause vitamin B12 deficiency, except:
   A. Lead poisoning
   B. Blind loop syndrome
   C. Post gastrectomy
   D. Pelvic radiation
4. A 82-year-old female was referred by her primary-care physician to the memory clinic with a 3–4-month history of forgetfulness, irritability, confusion and unsteady gait. Examination revealed pallor of the mucous membranes, smooth tongue, weakness of her lower limbs right more than left with increased tone, extensor plantar responses and loss of vibration sensation. The upper limbs were near normal. She had mild cognitive impairment. Haemoglobin: 10 G/L

   Which of the following is most likely:

   A. Alzheimer's disease
   B. Folate deficiency
   C. Vitamin B12 deficiency with subacute combined degeneration
   D. Spinal cord compression
   E. Multiple sclerosis

   Comment: In B12 deficiency neurological involvement may present in the absence of anaemia. Initially the central white matter followed by the peripheral nerves and thereafter the posterior and lateral columns (subacute combined degeneration) are involved. Folate deficiency does not cause SCD.

   Clinical manifestations

5. A 79-year-old female presented with shortness of breath, numbness and tingling of her extremities. She had pallor of the mucous membrane, loss of taste, sore tongue, mild jaundice and

splenomegaly. The blood pressure was 130/80 mmHg supine and 90/60 mmHg on standing. She had weakness of her lower limbs, diminished reflexes, reduced sensation of the extremities and unsteady gait.

Haemoglobin, 60 g/L; blood smear, oval macrocytes, hypersegmented neutrophils and 'aged neutrophils (shift to the right).

What is the most likely diagnosis?

A. Idiopathic peripheral neuropathy
B. Vitamin B12 deficiency
C. Guillain-Barre syndrome
D. Cord compression

6. In the management of B12 deficiency, the following are true, except:
   A. Prescribe folic acid 1 mg/daily with vitamin B12.
   B. Administer vitamin B12 1,000 mcg IM 2–4 weeks until haematological abnormalities return to normal and then once a month/for neurological symptoms if present, 1,000 mcg twice a month for 6 months and continued monthly.
   C. If untreated irreversible neurological damage can occur.
   D. Request for reticulocyte count in 3–4 days.

   Comment: In a patient with B12 deficiency, giving folic acid will exacerbate neurological deficits.

7. The following are characteristic features of pernicious anaemia, except:
   A. Presence of parietal cell and intrinsic factor antibodies.
   B. Schilling test usually returns to normal with intrinsic factor.
   C. Serum bilirubin and lactic dehydrogenase level are low.
   D. Marrow aspiration shows megaloblastic erythropoiesis.

MCQ Answers

1=D; 2=D; 3=A; 4=C; 5=B; 6=A; 7=C

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Myelodysplastic Syndromes

26

Contents

Abstract

Myelodysplastic syndromes (MDS) are clonal haemopoietic stem cell disorders in which the haemopoietic process is ineffective resulting in cytopenias, morphologic dysplasia and progression to acute myeloid leukaemia. MDS is primarily a disease of the elderly, and the mean age varies from about 60 to 75 years. The diagnosis should be considered in any patient with unexplained refractory anaemia and confirmed by hypercellular marrow with morphologically abnormal erythroblasts with or without the presence of ringed sideroblasts. The prognosis is highly variable and is dependent on the classification ranging from a few months to 15 years with a median survival of 3 years. Blood transfusion is the mainstay of treatment.

Keywords

Myelodysplastic syndromes · Clonal haemopoietic stem cell disorders · Unexplained anaemias · Refractory anaemia

Introduction

Myelodysplastic syndromes (MDS) are clonal haemopoietic stem cell disorders in which the haemopoietic process is ineffective [1] resulting in cytopenias, morphologic dysplasia and progression to acute myeloid leukaemia [2]. The incidence of MDS was 3.3 per 100,000 during the years 2001–2004 [3]. Myelodysplasia appeared to be the cause of unexplained anaemias (UA) in approximately 20% of these patients [4]. MDS is primarily a disease of the elderly with a median

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_27

age of 74 years [5]. Age is an important risk factor for the development of these disorders [6].

Clinical Manifestations

MDS is primarily a disease of the elderly, and the mean age varies from about 60 to 75 years [6]. The presentation is usually with symptoms of anaemia (fatigue, weakness and malaise), thrombocytopenia with bleeding manifestations(ecchymoses, nose bleeds) and/or fever associated with infection (UTI, pneumonia). Due to neutropenia even without significant thrombocytopenia, patients with myelodysplasia may be prone to bleeding [1] or infection because of platelet or neutrophil dysfunction. Other non-specific findings such as weight loss, anorexia and arthralgia may be present. There is a wide spectrum in its presentation, indolent to life threatening [6].

Diagnosis

The diagnosis should be considered in any patient with unexplained refractory anaemia and confirmed by hypercellular marrow with morphologically abnormal erythroblasts with or without the presence of ringed sideroblasts.The myeloid cells and megakaryocytes may show immaturity and are dysplastic. Diagnostic differentiation between MDS and AML can be problematical [7]. There are several MDS classifications, and the one that has gained acceptance is the French/American/British co-operative group (FAB) classification and requires more than or equal to 30% marrow or blast cells [8] for acute myeloid leukaemia (AML). The more recent World Health Organization classification requires only 20% blast cells for the diagnosis of AML [9]. The FAB recognizes five distinct forms of myelodysplasia based on the pathological findings, namely, (i) refractory anaemia (RA) with 5% bone marrow blast cells, (ii) refractory anaemia with excess blasts (RAEB) with 5–20% in the marrow, (iii) refractory anaemia with ringed sideroblasts (RARS) with 15% ringed sideroblasts, (iv) chronic myelomonocytic leukaemia (CMML) with monocytosis and $<5\%$ circulating blast cells and (v) refractory anaemia with excess blast cells in transformation (RAEB-T) with 20–30% blasts in the marrow and $>5\%$ in blood as defined by the FAB working group [8]. The World Health Organisation (WHO) has recommended to classify CMML in a separate group between myelodysplastic and myeloproliferative syndromes (MDS/MPS) [10]. The blood and marrow should be examined to define the specific FAB classification.

Prognosis

The prognosis is highly variable and is dependent on the classification ranging from a few months to 15 years with a median survival of 3 years. There are several prognostic scoring systems, and the one that has been widely used is the International Prognostic Scoring System (IPSS) and is based on the diagnostic cytogenetics, percentage of bone marrow myeloblasts and number of cytopenias [11]. The WHO Prognostic Scoring System is a more recent classification and categorises the prognosis into five risk groups, very low, low, intermediate, high and very high, showing different survivals and probabilities of leukaemic evolution [12, 13]. Those with ringed sideroblasts are less likely to progress to acute leukaemia.

Treatment

Blood transfusion is the mainstay of treatment. Recombinant human erythropoietin (rHuEPO) can be effective in MDS [6], and another erythropoietin-stimulating agent is darbepoetin alpha, and treatment with these may reduce the need for transfusions and improve quality of life [8]. Imatinib and lenalidomide have been found to be very effective in certain situations, but the overall clinical response rates in the more common MDS with any of the available agents are less than 20–30% [7]. According to Stone [7] in the older and frail individuals or who have indeterminate diagnostic features, a ‘watch-and-wait’ strategy seems feasible and should be the initial option

for a period before any decision as to the need for treatment is made. Patients with a bleeding tendency or documented platelet hypofunction [2] should not be given aspirin (and similar drugs). Platelet transfusion is indicated in those with bleeding or before surgery, and granulocyte growth factor (G-CSF) should be considered in neutropenic patients with gram-negative infections not responding to antibiotics alone. Chemotherapy in patients with excessive blasts has not improved survival. Bone marrow transplant may be suitable for younger age patients [5]. Early and enhanced transformation to frank acute leukaemic states had followed with the use of growth factors [5].

Acute myeloid leukaemia may occur with or without preceding or co-existing myelodysplasia. Patients with cytogenetic abnormalities involving chromosome7 and those with complex abnormalities have a poor prognosis, as do those with other significant comorbidities. Specific antileukaemia therapy may achieve a remission in 50–60% of patients [14].

Impact

See ▶ Chap. 29, "Lymphoproliferative Disorders"; Box 1.

Box 1 Key Points. Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) are clonal haemopoietic stem cell disorders in which the haemopoietic process is ineffective [1].

The prognosis is highly variable and is dependent on the classification ranging from a few months to 15 years with a median survival of 3 years.

There are several prognostic scoring systems. The WHO Prognostic Scoring System is a more recent classification and categorises the prognosis into five risk groups, very low, low, intermediate, high and very high, showing different survivals and probabilities of leukaemic evolution [12, 13].

Box 1 Key Points. Myelodysplastic Syndromes (continued)

Blood transfusion is the mainstay of treatment. Recombinant human erythropoietin (rHuEPO) can be effective in MDS [6].

Imatinib and lenalidomide have been found to be very effective in certain situations, but the overall clinical response rates in the more common MDS with any of the available agents are less than 20–30% [7].

In the older and frail individuals or who have indeterminate diagnostic features, a 'watch-and-wait' strategy seems feasible and should be the initial option for a period before any decision as to the need for treatment is made [7].

Multiple Choice Questions

1. The following are true of myelodysplastic syndromes (MDS), except:
   A. Blood transfusion is the mainstay of treatment.
   B. Imatinib and lenalidomide have been found to be effective.
   C. Recombinant human erythropoietin is not effective in MDS.
   D. Myelodysplastic syndromes are clonal haemopoietic stem cell disorders.

MCQ Answers

1 = C

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Myeloproliferative Neoplasms

27

Contents

Abstract

Myeloproliferative neoplasms (MPNs) formerly known as chronic myeloproliferative disorders are clonal haemopoietic stem cell disorders characterised by excessive production of mature blood cells. The classic MPNs are polycythaemia vera (PV), essential thrombocythaemia (ET), primary myelofibrosis (PMF) (Phi-negative) and chronic myelogenous leukaemia (CML), and the central role of protein tyrosine kinases in their pathogenesis have been identified. The hallmark for diagnosis of CML is demonstrating the presence of Philadelphia (Ph) chromosome in the bone marrow cells. This review provides an overview of the myeloproliferative neoplasms, their classification and their management.

Keywords

Myeloproliferative neoplasms · Chronic myelogenous leukaemia · Polycythaemia

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_28

vera · Primary myelofibrosis · Essential thrombocythaemia

Introduction

Myeloproliferative neoplasms (MPNs) formerly known as chronic myeloproliferative disorders are clonal haemopoietic stem cell disorders [1] characterised by excessive production of mature blood cells [2]. The World Health Organization system currently recognises eight types of MPN: chronic myelogenous leukaemia, chronic neutrophilic leukaemia, polycythaemia vera, primary myelofibrosis, essential thrombocythaemia, chronic eosinophilic leukaemia, mastocytosis and myeloproliferative neoplasm and unclassifiable [3]. The classic MPNs are polycythaemia vera (PV), essential thrombocythaemia (ET), primary myelofibrosis (PMF) (Phi-negative) and chronic myelogenous leukaemia (CML), and the central role of protein tyrosine kinases in their pathogenesis have been identified [4], and the new classification system embraces mutations discovered in the JA2 and MPL genes [5]. CML and other MPNs are classified on the basis of the presence or absence of the BCR-ABL1 fusion gene which is the hallmark of CML [6]. The BCL-ABL1-negative MPNs include PV, ET and PMF [7], and they are associated with three types of molecular markers, namely, activating mutations in the JAK2 gene, activating mutations in the MPL gene and alterations of CALR and the gene coding calreticulin (CALR) detected in ET and PMF [8–11]. A significant proportion of patients with PV, ET and PMF have been identified with JA2 tyrosine kinase (JAK2V617F) [1]. According to the Polycythaemia Vera Study Group (PVSG), the majority of PV patients are JAK2V617F positive on the polymerase chain reaction test (PCR), whereas only about 50% of the ET and PMF patients are positive [12].

Chronic Myeloid Leukaemia

Chronic myeloid (CML) is a clonal disorder with malignant transformation of a pluripotential stem cell resulting in an overproduction of granulocytes (immature and mature). It occurs frequently in young and middle-aged adults with slightly higher incidence in men. In 95% of the patients with CML, a chromosomal abnormality, the Philadelphia (Ph) chromosome, is present [13, 14], and this abnormality is present not only in the granulocytes but also in the erythrocytes and megakaryocytes indicating that CML arises from a pluripotential stem cell. The hallmark for diagnosis is demonstrating the presence of Philadelphia (Ph) chromosome in the bone marrow cells. In about 5% of the patients with CML, the Ph chromosome is not detected, and many of these patients with Ph-negative CML are found to have features consistent with myelodysplasia (chronic myelomonocytic leukaemia) [15, 16]. The presence of the Ph chromosome results in the synthesis of the breakpoint cluster region-Abelson murine leukaemia (BCR-ABL) fusion oncoprotein, a constitutionally active tyrosine kinase [17].

Clinical Manifestations

The symptoms may be non-specific and include fatigue, tiredness, weakness, weight loss, loss of appetite and fever and a feeling of fullness in the abdomen. There is moderate to massive enlargement of the spleen. There may be an acute onset pain due to infarction of the spleen. With progression of the disease, there are increasing pallor and bleeding manifestations, appearance of marked lymphadenopathy, fever, infection and skin involvement which are ominous signs.

Diagnosis

The peripheral white cell count could vary between 50 and 200 $\times 10^9$ per litre. In the peripheral blood, metamyelocytes predominate (Fig. 1). There may be anaemia or low platelet count. In the chronic phase, the peripheral blast count is less than 10%. Diagnostic confirmation is by karyotypic demonstration of the Philadelphia chromosome.

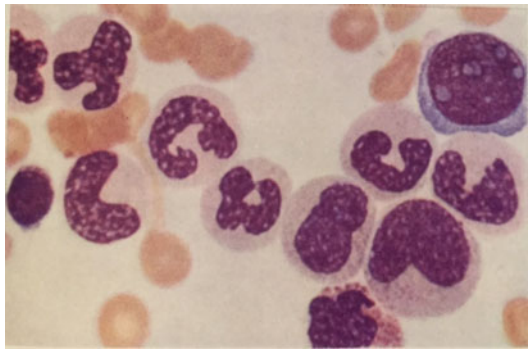


Fig. 1 Chronic myelocytic leukaemia (Reproduced with kind permission from Norvatis Company Archives, 'Sandoz Atlas of Haematology' FA Sandoz, 1973)

Treatment

The treatment options will depend on the patient's age and the state of the overall health. CML can be treated with bone marrow transplant, drug therapy or both. There a number of newer targeted biological therapies showing promise. Interferon-alpha (IFN-a) and cytarabine have a limited response rate by prolonging survival on average by only a year or two [18]. Currently the preferred first-line therapy comprises imatinib, a tyrosine kinase inhibitor (TKI) which targets the disease process at the molecular level (i.e. BCR-ABL transcription) [17, 19]. It had been estimated that patients responding to imatinib have a prognosis of more than 20 years [20]. Some of the patients develop resistance or toxicity [17]. More recently the more potent TKIs, nilotinib and dasatinib have been evaluated for their efficacy and safety. They lend an effective option for patients who develop problems with imatinib and the newer TKIs may be considered as first-line therapy over imatinib [17, 19]. The only other known treatment which is potentially curative is allogeneic stem cell transplant [18]. The anaemia and bleeding can be treated with blood transfusions. The bacterial infections require urgent intravenous antibiotics. The destruction of the leukaemic cells can produce large amounts of uric acid which will require prophylactic treatment with allopurinol.

Polycythaemia Vera

Polycythaemia vera (PV) is a stem cell clonal disorder in which there is an increased production of red blood cells, increased white blood cells and platelets without significant bone marrow fibrosis [21] together with splenomegaly, hypercellular marrow with hyperplasia of all cell lines. It occurs more often in males, and the peak incidence is between the ages of 50 and 70 years [22].

Clinical Manifestations

Some of the patients are asymptomatic, and symptoms are often insidious in onset. There is an increase in the red cell mass resulting in hyperviscosity, and symptoms are related to the hyperviscosity, thromboses and sludging of blood flow. Symptoms relating to hyperviscosity include light headedness, dizziness, headache, tinnitus, fatigue and tiredness (Box 1). A classic symptom is pruritus especially after exposure to warm water after a hot bath [23]. There is a high incidence of thrombotic events resulting in venous thrombosis, thromboembolism and Budd-Chiari syndrome [24]. The incidence of bleeding varies, and 12–15% of persons with bleeding in PV are due to acquired von Willebrand syndrome [22]. Abdominal pain can be due to peptic ulcer or splenic infarction.

Box 1 Sequelae to Polycythaemia Vera

I. Life-threatening
   Stroke, evolution into myelofibrosis with myeloid metaplasia, evolution into acute leukaemia
II. Non-life-threatening
   Pruritus, hyperuricaemia, gout, bleeding, disordered sensorium, microvascular complications, headache, lightheadedness, dizziness, transient ischaemic attack, transient ocular disturbances, paraesthesia, digital ischaemia and erythromelalgia Information sources: [23, 25]

Differential Diagnosis and Diagnosis

The diagnosis of polycythaemia vera is based on clinical criteria (Table 1) defined by either the Polycythaemia Vera Study Group or the World Health Organization [26]. In polycythaemia vera (PV), the haemoglobin (more than 180 g per L) and haematocrit levels are elevated. Absolute erythrocytosis is confirmed by measurement of the red cell mass by radioisotope techniques which are not always available in most places. Often the finding of an elevated haematocrit is the first indication of polycythaemia. A haematocrit greater than 60% in the absence of dehydration is always associated with polycythaemia. Haematocrit values between 50% and 60% require direct measurement of the red blood cell mass for the diagnosis of polycythaemia [27]. The elevated haematocrit could be due to either increased production of red blood cells by the bone marrow or from haemoconcentration (relative polycythaemia). Measurement of serum Epo level should be considered as first intention diagnostic test for patients with absolute erythrocytosis [26]. Serum Epo level was found to be below the normal range in the majority of patients with PV compared to those with secondary erythrocytosis [26].

More than 90% of PV patients carry JAK2V617F. It is recommended that the recent discovery of JAK2V617F which is present in more than 90% of patients with PV the peripheral blood mutation screening for the mutation should be included in the eventual evaluation of patients with suspected PV [28, 29]. After confirming the diagnosis of polycythaemia, the diagnostic issue is to distinguish PV from other causes of erythrocytosis which are more common than PV (see Algorithm 1). The laboratory differences between polycythaemia and secondary polycythaemia are shown in Table 2.

Table 1 Criteria for diagnosis of polycythaemia vera

Category A	Category B
Increased red cell mass	Thrombocytosis >400 × 10 uL
Males >36 ml/kg	Leucocytosis >12 × 10 uL
Females >32 ml/kg	Leucocyte alkaline phosphatase (LAP) >100
Arterial oxygen saturation >92%	Serum B12 concentration >900 ug/ml or binding capacity greater than 2
Splenomegaly	

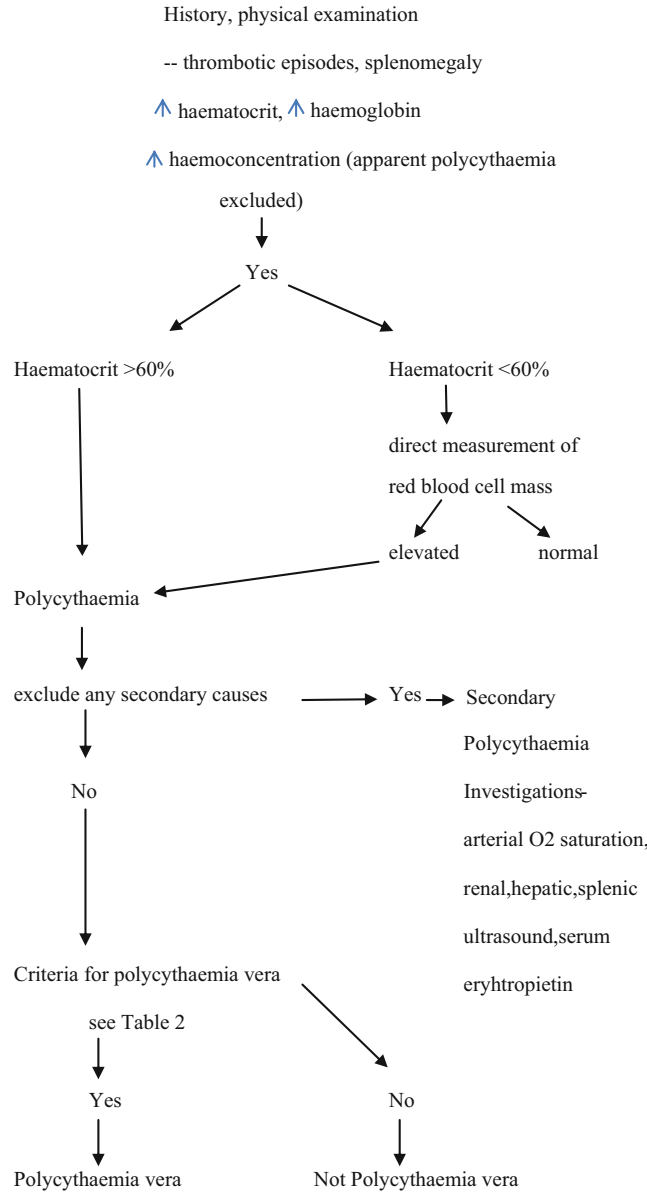
Diagnosis is established with all three in Category A or 2 in Category A plus two in Category B
Source of information: Besa and Woermann [22]

Treatment

The aims of treatment are (i) to reduce the haematocrit to <45 and (ii) to reduce the platelet count to <400 × 10 9 L.

Treatment is based on a risk stratification approach and is individualised. The risk stratification is categorised into low, intermediate and high risk based on the age above or below 60 years, the history of thrombotic events and the platelet count. The higher the platelet count, the greater the risk [30]. The mainstay of treatment is phlebotomy and aspirin [25] in low-risk patients which is tailored according to the patient's needs. Patients with a haematocrit value of less than 70% may be bled twice a week, and those with severe plethora with altered mentation or vascular comprise may be bled more vigorously [22] and eventually reduced to once in 6–10 weeks in most patients.

Treatment with hydroxyurea (HU) (hydroxycarbamide) is added to reduce the hypermetabolic symptoms, to control the platelet count and to shrink the enlarged spleen. Randomised studies demonstrated the HU is effective in preventing thrombosis and should be considered as a drug of choice in high-risk patients [25]. In the elderly, intermittent low-dose oral busulphan is often more convenient with potential side effects more acceptable [31]. Interferon-alpha is another option to reduce the red cell burden and treating PV-associated pruritus, but there is a high incidence of side effects [25]. Radioactive phosphorus (32p) carries the risk of inducing malignancies such as acute leukaemia but may be used in the elderly where attendance, compliance and venous access are poor [31]. Anagrelide hydrochloride lowers platelet levels, but thrombocytopenia appears to be the main dose-limiting adverse



Algorithm 1 for the evaluation of a patient with elevated haematocrit in whom history and physical examination suggests polycythaemia

effect. Several Janus kinase inhibitors are on trial for polycythaemia vera, essential thrombocythaemia and myelofibrosis. Tyrosine kinase inhibitor imatinib has been shown to be effective in lowering the platelet counts, reducing splenic size and reducing the need for phlebotomy [25]. Ruxolitinib a JAK1and JAK2 inhibitor has undergone trials in patients with PV, ET and PMF [7]. Low-dose aspirin is recommended in patients without a history of GI bleeding [32].

Symptomatic Treatment

i. Pruritus – H1 and H2 blocking antihistamines, interferon-alpha, myelosuppressive agents, ultraviolet light, oatmeal and starch baths
ii. Hyperuricaemia and gout – allopurinol (100–300 mg/daily) until remission, for acute gout anti-inflammatory agents
iii. Thrombosis-antiplatelet drugs – aspirin, dipyridamole and, in proven thrombotic complications, warfarin

Table 2 Laboratory evaluation in polycythaemia

Laboratory investigation	Polycythaemia vera	Secondary polycythaemia
Total red cell volume	Increased	Increased
Arterial O2 saturation	Normal	Decreased
White blood cells	Increased	Normal
Platelet count	Increased	Normal
Leucocyte alkaline phosphatase (LAP)	Increased	Normal[a]
Vitamin B12 level	Increased	Normal
Unbound B12	Increased	Normal
Erythropoietin level	Decreased	Increased or normal

[a]Inflammation or infection may elevate LAP

iv. Erythromelalgia (burning, pain in feet, hands and may proceed to gangrene) – myelosuppressive therapy + phlebotomies, aspirin and dipyridamole

Prognosis

In the treated patient long survival of more than 16 years. Twenty percent of them transform to myelofibrosis and 5% to acute leukaemia [25]. The incidence of acute leukaemia is increased in those with myelofibrosis, use of P_{32} and high-dose cytotoxic agents. Other causes of morbidity and mortality are thrombosis, peptic ulcer disease and haemorrhagic complications.

Essential Thrombocythaemia

There is an increased production of platelets giving rise to markedly increased in platelet counts. It is rare with a low incidence and high prevalence [32] and occurs more often in males, and the peak incidence is between the ages of 50 and 70 years. JAL2(V617F)-positive ET comprises three phenotypes at clinical and bone marrow level based on WHO definition [12].

Clinical Manifestations

The clinical course is characterised by a predisposition to thromboembolic events and less commonly to bleeding manifestations which are relatively mild. The symptomatology is variable ranging from one of event-free course to one of life-threatening outcomes. There is a risk of occlusive vascular lesions and digital ischaemia, and gangrene of the toes may be seen. Splenomegaly occurs in about 60% of the patients.

Diagnosis

The diagnosis of ET is by exclusion. Other causes of elevated platelet counts (Box 2) should be excluded before the diagnosis of ET can be made. The platelet count is usually more than 1 million/uL. Table 3 shows the diagnostic requirements for the myeloproliferative disorders. The predictive positive value of JAK2(V617F) PCR test is about 50% for ET [12].

Box 2 Causes of Elevated Platelet Counts

i. Reactive thrombocytosis
   - Acute infection
   - Chronic inflammatory disorders – rheumatoid arthritis, inflammatory bowel disorders
   - Malignant diseases
   - Splenectomy

ii. Essential thrombocythaemia
iii. Polycythaemia vera
iv. Myelofibrosis
v. Chronic myeloid leukaemia

Table 3 summarises the distinguishing features of chronic myeloid neoplasms.

Treatment

The aim of treatment is to reduce the platelet level and relieve symptoms. The indications for therapy are unclear. Risk stratification based on the clinical criteria such as age, platelet count and history of previous ET-related events may help to define patients at risk [33]. Low-risk patients with ET are

Table 3 Distinguishing features of chronic myeloproliferative neoplasms

		Essential thrombocythaemia leukaemia	Polycythaemia vera	Myelofibrosis chronic myeloid
Platelet count	Markedly elevated	Moderately elevated	Mildly elevated	Moderately elevated
Red cell mass	Decreased	Increased	Decreased	Decreased
White cells	Normal/increased	Increased	Variable	Markedly increased
Blood picture	Platelet aggregates, giant platelet	–	'Teardrop' red cells	Entire myeloid series
Bone marrow	Hyperplasia megakaryocytic	Hyperplasia erythroid	Hyper-/hypo-cellularity + fibrosis	Hypercellular myeloid
Philadelphia chromosome	Negative	Negative	Negative	Positive
Leucocyte alkaline phosphatase score	Normal/elevated	Markedly elevated	Variable	Very low

best left untreated [97]. Patients with a platelet count of 600 × 10/l and who are asymptomatic may not require any treatment, but in those with higher platelet counts or with thrombotic or haemorrhagic complications, therapy is indicated. Myelosuppressive therapy is indicated in high-risk patients. Cytoreductive drugs – hydroxyurea, pipobroman, IFN-a, pegylated IFNs or anagrelide – are therapeutic options [33]. For patients over the age of 60 years, hydroxyurea may be the best therapeutic option with regard to efficacy and cost [33]. Interferon-alpha has been used and may control the platelet count so does anagrelide. The latter is not toxic to the bone marrow and its side effects are mild. For immediate reduction of platelet count, plateletpheresis has been used. Hydroxycarbamide and anagrelide are the most used drugs and low-dose aspirin as an anti-aggregative drug [32]. The identification of the JAK2V617F raises the possibility of molecular targeted therapy [25].

Myelofibrosis and Myeloid Metaplasia

Idiopathic myelofibrosis also known as agogenic myeloid metaplasia is a clonal stem cell disorder [34]. The peak of incidence is between 50 and 70 years with a median age of approximately 65 at diagnosis, and there are no differences with regard to gender [35].

Clinical Manifestations

In the early stages the patients may be asymptomatic [36] and the abnormal blood findings or splenomegaly may be a chance finding. Enlargement of the liver follows. In the later stages, anaemia-related symptoms, malaise, weakness, night sweats, breathlessness and weight loss are evident or splenomegaly-related symptoms such as pain due to splenic infarction, abdominal discomfort especially postprandial, satiety and diarrhoea together with haematological manifestations such as bleeding gums, epistaxis, bruising, gastrointestinal bleeding or cerebral haemorrhage.

Diagnosis

The peripheral blood smear shows teardrop red blood cells and a leucoerythroblastic picture with circulating nucleated red cells together with immature white cells with prominent metamyelocytes and myelocytes [34]. The platelets may be decreased or increased and are large. The lactate dehydrogenase level is raised [34] and has been attributed to deficient haemopoiesis. The bone marrow aspiration results in a dry tap. Core biopsy reveals medullary fibrosis, dysplastic megakaryocyte hyperplasia and dilated marrow sinuses [34]. The positive predictive value of a JAK2(V617F) PCR test is about 50% [12].

Prognosis

The median survival is between 3.5 and 5.5 years [35, 37], but the patient without significant anaemia (Hb >10 g/dl) has a median survival of 10 years or more [30]. The main causes of death are infection, leukaemic transformation, heart failure and thrombohaemorrhagic events attributable to platelet dysfunction [38].

Treatment

There is no cure. The asymptomatic requires no treatment. Splenectomy, chemotherapy (hydroxyurea) and radiotherapy in certain cases are palliations. Packed red cell transfusion if the erythropoietin levels are low may be given to help minimise the new select group of patients [34]. In Australia ruxolitinib a Janus kinase inhibitor has been approved for myelofibrosis, and treatment resulted in durable reductions in splenomegaly and betterment in disease-related symptoms [7], but treatment with ruxolitinib can be limited by significant anaemia [39] and thrombocytopenia but is manageable [7] (Box 3).

Box 3 Key Points. Myeloproliferative Neoplasms

Chronic myeloid leukaemia

In 95% of the patients with CML, a chromosomal abnormality, the Philadelphia (Ph) chromosome, is present [13, 14].

CML could be treated with bone marrow transplant, drug therapy or both. Interferon-alpha (IFN-a) has a limited response rate [18].

The presence of the Ph chromosome results in the synthesis of the breakpoint cluster region-Abelson murine leukaemia (BCR-ABL) fusion oncoprotein, a constitutionally active tyrosine kinase [17].

Currently the preferred first-line therapy comprises imatinib, a tyrosine kinase inhibitor (TKI) which targets the disease process at the molecular level (i.e. BCR-ABL transcription) [17, 18].

Polycythaemia vera

The mainstay of treatment is phlebotomy which tailored according to the patient's need.

In the elderly, intermittent low-dose oral busulphan is often more convenient with potential side effects more acceptable [31].

Tyrosine kinase inhibitor imatinib has been shown to be effective in lowering the platelet counts, reducing splenic size and reducing the need for phlebotomy [25].

Low-dose aspirin is recommended in patients without history of GI bleeding [31].

Essential thrombocythaemia

Cytoreductive drugs – hydroxyurea, pipobroman, IFN-a, pegylated IFNs or anagrelide – are therapeutic options for essential thrombocythaemia [34].

For patients over the age of 60 years, hydroxyurea may be the best therapeutic option.

Plateletpheresis has been used.

Hydroxycarbamide and anagrelide are the most used drugs and low-dose aspirin as an antiaggregation drug [31].

Myelofibrosis and myeloid metaplasia

There is no cure. The asymptomatic requires no treatment.

Splenectomy, chemotherapy (hydroxyurea) and radiotherapy in certain cases are palliations.

Packed red cell transfusion if the erythropoietin levels are low is administered.

Ruxolitinib a JAK1and JAK2 inhibitor has undergone trials in patients with PV, ET and PMF [7].

Ruxolitinib treatment resulted in durable reductions in splenomegaly and betterment in disease-related symptoms [7].

Low-dose aspirin is recommended in patients without a history of GI bleeding [32].

Multiple Choice Questions

1. Lymphadenopathy together with splenomegaly is a usual finding in the following conditions EXCEPT
   A. Infectious mononucleosis
   B. Chronic leukaemia in the acute phase
   C. Chronic lymphatic leukaemia
   D. Multiple myeloma
2. A 75-year-old female presented with weakness, headache, fatigue, breathlessness and visual disturbances. The diagnosis is polycythaemia vera. Which of the following support the diagnosis?
   A. Elevated haemoglobin, white cell count and platelets.
   B. Decreased leucocyte alkaline phosphatase score.
   C. Splenomegaly.
   D. Increased blood viscosity.
3. The patient has chronic granulocytic leukaemia. The following findings are related to the patient's condition EXCEPT:
   A. A markedly enlarged spleen.
   B. The Philadelphia (Ph) chromosome can be demonstrated in less than 5% of the patients.
   C. The appearance of marked lymphadenopathy, fever, infection and skin involvement are ominous signs.
   D. Patients responding to imatinib have a prognosis of more than 20 years.
4. The patient has myelofibrosis. The following are consistent with the disease, EXCEPT:
   A. Blood smear shows teardrop cells.
   B. Bone marrow aspiration results in a dry tap.
   C. The median survival is between 3.5 and 5 years.
   D. Erythropoietin level may be high.

MCQ Answers

1 = D; 2 = B; 3 = B; 4 = D

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Immunoproliferative Disorders

28

Contents

Abstract

Multiple myeloma (MM) is a B-cell neoplastic disease characterized by excessive number of abnormal plasma cells in the bone marrow and overproduction of intact monoclonal immunoglobulins or light chain (Bence Jones) proteins. The average age of onset is about 60 years and occurs more frequently in men than women. MM is preceded by a premalignant condition termed monoclonal gammopathy of undetermined significance (MGUS). Age is an important prognostic factor, and with each decade from the age of 50 years to over the age of 80, the overall survival declines. This review will provide an update on the clinical management of multiple myeloma.

Keywords

Multiple myeloma · Monoclonal gammopathy of undetermined significance (MGUS) · Bence Jones proteins · B-cell neoplastic disease

Introduction

Multiple myeloma is a B-cell neoplastic disease characterized by excessive number of abnormal plasma cells in the bone marrow and overproduction of intact monoclonal immunoglobulins or light chain (Bence Jones) proteins.The cause is not known and the epidemiological pattern remains obscure [1]. Age is the most significant risk factor. Genetic factors, certain viruses, certain chemicals and radiation and certain occupations have been suggested as possible associations in its causation. It is possible that many factors acting together result in myeloma.

Clinical Manifestations

The average age of onset is about 60 years and occurs more frequently in men than women. Because of its effects on the bone, bone marrow and kidney,

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_25

the clinical features are osteolytic lesions, anaemia, renal insufficiency and recurrent bacterial infections [2] (Box 1). Physical examination reveals pallor, bone tenderness, ecchymosis, papules, nodules, neurological deficits, extramedullary plasmocytomas and amyloidosis (macroglossia, shoulder pad sign – bilateral swelling of the shoulder joints due to deposition of amyloid). X-ray of the bones may show typical punched-out lytic lesions (Fig. 1) or diffuse generalized osteoporosis. MM patients are prone to develop deep vein thrombosis and venous thromboembolism [3]. About one-fifth of the patients at the time of diagnosis will have renal insufficiency, and about half over the course of the disease will have renal dysfunction [4, 5].

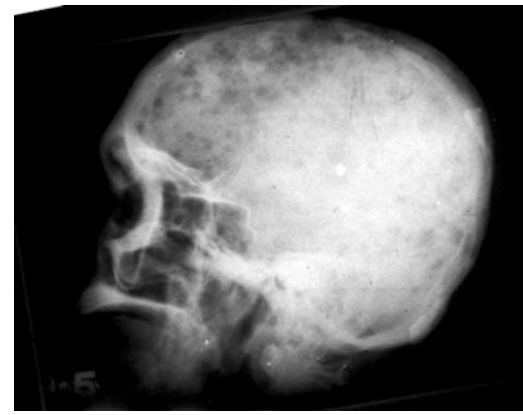

Fig. 1 Lateral view of the skull with changes due to multiple myeloma showing numerous punched-out osteolytic areas

Box 1 Clinical Symptoms of Multiple Myeloma

Bone

- Pain, pathological fractures
- Localized tumours (plasmocytomas)

Blood

- Bleeding manifestations
- Hypercalcaemia
- Hyperviscosity

Renal insufficiency

Neurological

- Spinal cord compression
- Carpal tunnel syndrome
- Peripheral neuropathy

Infection

- Bacterial (recurrent)

Information sources: [2, 4, 5].

MM is preceded by a premalignant condition termed monoclonal gammopathy of undetermined significance (MGUS) [6]. MGUS is marked by the presence in the serum of less than 30 g/l of monoclonal IgG and IgA without any other evidence of multiple myeloma, i.e. bone marrow plasmacytosis, lytic bone lesions and decreased levels of normal immunoglobulins. Long-term follow-up (for 30 years or more) of patients have shown that multiple myeloma develops in up to 16% with an annual actual risk of 0.8% [7].

Diagnosis

The basic tests include a full blood count, creatinine, uric acid, electrolytes and sedimentation rate. All patients are screened with electrophoresis of serum and urine. Immunofixation of the paraprotein band enables to identify the immunoglobulin isotype of the paraprotein. Bone scanning lacks specificity for myeloma and is not a suitable alternative for radiological examination [8]. Bone marrow aspiration is a decisive procedure in establishing a definite diagnosis of myeloma (Fig. 2). The criteria for the diagnosis of MM is based on the clinical manifestations of end organ damage and is referred to as CRAB [4]: (i) hypercalcaemia, a serum calcium level more than 2.75 mmol/L; (ii) renal insufficiency, creatinine more than 173 mmol/L; (iii) anaemia, haemoglobin less than 10gm/dL; and (iv) bone lesions [4].

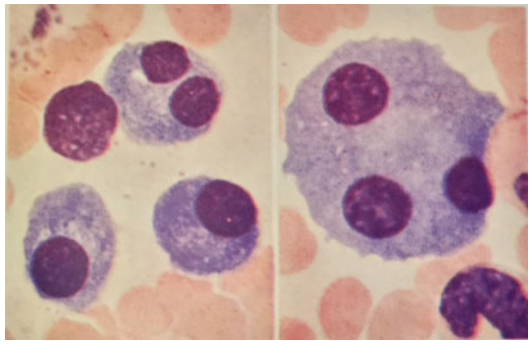

Fig. 2 Bone marrow showing polypoid plasma cells. Reproduced with kind permission from Norvatis Company Archives, *Sandoz Atlas of Haematology* FA Sandoz,1973

Prognosis

Age is an important prognostic factor, and with each decade from the age of 50 years to over the age of 80, the overall survival declines [9]. The total mass of myeloma cells correlate directly with the bone lesions, hypercalcaemia and anaemia and have prognostic value [10, 11]. In unselected patients, the prognosis is 2.5–3 years (median survival) [12]. A Mayo Clinic study revealed that plasma cell labelling index, levels of thymidine kinase, beta-2 macroglobulin, serum albumin and C-reactive protein and age were significant univariate prognostic factors [12]. Beta-2 microglobulin is a strong predictor of outcome and a marker for the overall body tumour burden. Beta-2 microglobulin and C-reactive protein together have been used to estimate prognosis in terms of median survival. If both levels are below 6 mg/l, the survival is 54 months; if one component is less than 6 mg/l, it is 27 months; and if both are greater than 6 mg/l, it is 6 months [13]. CRP is useful to gauge prognosis as CRP is a surrogate marker of interleukin-6 and is often referred to as plasma cell growth factor [13] Serum immunoreactive IL-6 is a significant prognostic marker in multiple myeloma, and high level is regarded as a predictor of poor prognosis [14]. It should be noted, however, that beta-2 microglobulin may be raised in renal failure and C-reactive protein may be raised due to infective or inflammatory disorders. Myeloma can be staged using the Durie–Salmon staging system [15] which is divided into three stages – low-, intermediate- and high-class cell mass – and based on the severity of the anaemia, calcium level, renal failure, presence or absence of bone lesions and the quantity of abnormal proteins using clinical parameters that predicted myeloma cell tumour burden. It is useful as a measure of prognosis. The International Staging System for multiple myeloma relies mainly on the level of albumin and beta-2 microglobulin and is regarded as a simple and reliable predictor of survival duration [16–19]. Cytogenetic data contributes to significant prognostic information although the yield is low [3].

Treatment

In patients without comorbidities (cardiovascular or significant renal impairment) and under 65 years of age, the aim of treatment is to improve survival with an autograft which consists of a 3–6 months of induction therapy aimed at reducing tumour load and contamination of stem cell harvests by malignant cells [20] followed by autologous stem cell transplantation (ASCT). A second stem cell transplantation 3–6 months after the first is given for those who did not have a full response to the first [21] (Fig. 3). Patients who are very much older and with significant comorbidities may be treated with oral chemotherapy (melphalan or cyclophosphamide and prednisolone). However, ASCT is practical in selected patients older than 65 years with good functional status without severe comorbidities [23]. Novel therapeutic agents (immunomodulatory drugs thalidomide and lenalidomide and protease inhibitor bortezomib) are now increasingly used in the treatment of MM and the superiority of adding one novel agent to melphalan plus prednisone [22]. Randomized controlled trials show that in the elderly who are not eligible for transplant, the addition of thalidomide to melphalan and prednisolone results in response rates superior to melphalan and prednisolone alone [23]. Recent studies have shown a good response in a high

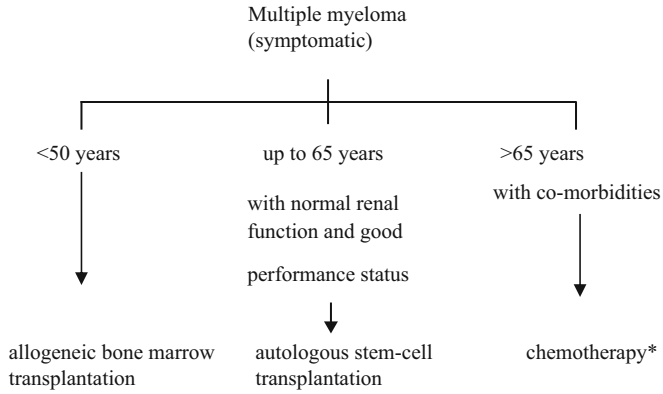

Fig. 3 Treatment of multiple myeloma based on age and comorbidities (Information source: Attal et al. [25]; Harousseau [22])

proportion of patients treated with targeted therapies.

New targeted drug therapies include three drugs: thalidomide, its analogue lenalidomide and the proteasome inhibitor bortezomib [24]. Neuropathy is a major side effect with thalidomide and bortezomib and myelotoxicity with lenalidomide [24]. Thalidomide and dexamethasone have been shown to be as effective for induction before stem cell transplantation as standard therapies [24]. Thalidomide taken after stem cell transplantation prolongs event-free survival and prevents relapse as compared with no therapy [25]. Treatment with interferon alfa is controversial.

Lytic bone disease, bone pain and hypercalcaemia are common clinical manifestations of myeloma. Myelomatous bone disease can be treated or even prevented with bisphosponate therapy. An uncommon side effect of this agent is osteonecrosis of the jaw [24, 26, 27] (Fig. 3).

Impact

See ▶ Chap. 29, "Lymphoproliferative Disorders"; Box 2

Box 2 Key Points. Multiple Myeloma

Because of its effects on the bone, bone marrow and kidney, the clinical features are osteolytic lesions, anaemia, renal insufficiency and recurrent bacterial infections [2].

Box 2 Key Points. Multiple Myeloma (continued)

Age is an important prognostic factor, and with each decade from the age of 50 years to over the age of 80, the overall survival declines [9].

Patients who are very much older and with significant comorbidities may be treated with oral chemotherapy (melphalan or cyclophosphamide and prednisolone).

However, ASCT is practical in selected patients older than 65 years with good functional status without severe comorbidities [23].

New targeted drug therapies include three drugs: thalidomide, its analogue lenalidomide and the proteasome inhibitor bortezomib [24].

Multiple Choice Questions

1. A 70-year-old man complained of fatigue, tiredness, weakness and low back pain over 3–4 months. Routine blood smear showed normocytic normochromic anaemia with rouleaux formation. The sedimentation rate was markedly increased. The diagnosis was multiple myeloma.

   The following would be consistent with the patient's illness, except:

   A. Beta-2 microglobulin is elevated.
   B. X-ray of bones shows generalized osteoporosis.

C. Serum level of monoclonal protein is >30 g/L.
D. Serum electrophoresis shows polyclonal pattern.

2. The following are associated with paraproteinaemia, except:
A. Chronic granulocytic leukaemia
B. Chronic lymphatic leukaemia
C. Primary amyloidosis
D. Macroglobulinaemia

MCQ Answers

1 = D; 2 = A

Short Answer Questions

1. List four clinical and laboratory findings for the diagnosis of multiple myeloma.

SAQ Answers

1. Peak incidence between 60–70 years
2. Blood marrow plasmacytosis of >10%
3. Multiple osteolytic lesions on X-ray
4. Bence Jones proteinuria

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Lymphoproliferative Disorders

29

Contents

Abstract

This review discusses the lymphoproliferative disorders, their prevalence and clinical management. Chronic lymphocytic leukaemia (CLL) is derived from mature B lymphocytes and is characterised by a progressive accumulation of lymphocytes in the blood, bone marrow and lymphatic tissues. CLL is a disease of the elderly. Antileukaemic therapy is frequently unnecessary in uncomplicated early disease. Non-Hodgkin's lymphoma includes a diverse group of haematological causes which embraces any lymphoma other than Hodgkin's lymphoma and by the absence of Reed-Sternberg cells. Hodgkin's lymphoma (HL) is a malignant tumour of the lymphatic tissues and weakens the immune system.

Keywords

Lymphoproliferative disorders · Chronic lymphocytic leukaemia · Non-Hodgkin's lymphoma · Hodgkin's lymphoma · Reed-Sternberg cells

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_26

Chronic Lymphatic Leukaemia

Introduction

Chronic lymphocytic leukaemia (CLL) is derived from mature B lymphocytes [1] and is characterised by a progressive accumulation of lymphocytes in the blood, bone marrow and lymphatic tissues. CLL is a disease of the elderly which increases with advancing age [2] and is twice as common in men. It is the most common form of leukaemia in adults in the Western countries [3]. Ninety-five percent of the CLL in the United States is of B-cell type, and the T-cell type prevails in occidental countries [3, 4]. The overall incidence rate in the United States is 2.3 per 100,000 [5, 6].

Clinical Manifestations

The presenting symptoms and signs of CLL are extremely variable. In about 40–60% of the patients, the lymphocytosis is an incidental finding [7], and even when progressive, some patients may remain asymptomatic for years. The symptomatic patients have non-specific complaints of fatigue, weight loss, dyspnoea on exertion, enlarged lymph nodes and abdominal features. On physical examination, there is generalised lymph adenopathy (small, discrete, non-tender nodes), and there is minimal to moderate enlargement of the liver and spleen. As the disease progresses signs of anaemia, thrombocytopenia or pancytopenia may occur with clinical haemorrhage or infection, the latter being a frequent cause of death [8]. Infections are usually pyogenic due to the immunodeficiency (depressed immunoglobulin levels). Patients may also develop immune-mediated cytopenias such as Coombs positive haemolytic anaemia and immune thrombocytopenia [9–11].

Diagnosis

The minimal requirement is a sustained absolute lymphocyte count of >5,000 ul [12], and lymphocyte counts in the blood are usually equal to or higher than 10,000 ul [13], and they consist of well-differentiated lymphocytes. The bone marrow aspiration should show more than 30% of all nucleated cells to be lymphoid [7] but may not be needed for diagnosis. The diagnosis in most cases could be confirmed by lymphocyte surface marker studies on a specimen of peripheral blood showing monoclonality. The differential diagnosis includes hairy cell leukaemia, non-Hodgkin's lymphoma, Waldenstrom's macroglobulinaemia and viral infections. Reactive lymphocytosis due to viral infections can be differentiated by the clinical picture, the presence of atypical lymphocytes on the blood smear and the absence of lymphocyte monoclonality. Waldenstrom's macroglobulinaemia is characterised by the presence of elevated monoclonal immunoglobulin M. The cells of the hairy cell leukaemia (cytoplasmic projections) and that of Sezary syndrome (cerebriform nuclei) are distinctive.

Prognosis

The overall 5-year survival is approximately 60% but depends on the stage of the disease [3]. Clinical staging is useful for prognosis and treatment. The Rai staging is based on the haematological changes [14] (Table 1). Stages III and IV are more likely to die in 1–2 years [15]. Most patients with CLL die of infections usually bacterial sometimes fungal or mycobacterial. CLL patients are also more prone to second malignancies.

Treatment

Antileukaemic therapy is frequently unnecessary in uncomplicated early disease [3]. Stages 0–II

Table 1 Staging [14] in chronic lymphatic leukaemia

Stage	
0	Absolute lymphocytes >10,000u/L
	+30% lymphocytes in marrow
I	0+ lymph nodes
II	I + enlarged spleen and/or liver
II	II + anaemia
IV	III + thrombocytopenia (platelets<100,000u/L)

may stay alive without treatment for 5–20 years. For stages III–IV, initial therapy is usually with an alkylating agent such as chlorambucil, and it remains extensively used in the elderly [15]. Fludarabine is now considered a therapeutic option for initial treatment [7]. The current FCR (fludarabine, cyclophosphamide and the anti-CD20 monoclonal antibody rituximab) has been shown to result in significant increase in complete remissions [16]. Obinutuzumab is a humanised monoclonal antibody, plus chlorambucil has been shown to prolong progression-free survival by 15 months compared to chlorambucil alone [17]. In relapsed CLL, both allogenic and autologous transplants have been used in its management [18]. Supportive care-blood and platelet transfusions, antibiotics, antiviral drugs, gamma-globulin infusions, corticosteroids (Coombs positive haemolytic anaemia, immune thrombocytopenia) and radiotherapy to areas of lymphadenopathy.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma includes a diverse group of haematological causes which embraces any lymphoma other than Hodgkin's lymphoma and by the absence of Reed-Sternberg cells. The incidence of non-Hodgkin's lymphoma is increasing by an average of 6.8% per annum [19], and it increases with age.

Symptomatology

The follicular lymphoma occurs in their 60s and in equal frequency in both sexes. The adenopathy is often generalised, and persistent lymphadenopathy may be the first presentation. Systemic symptoms may be seen in some, and symptoms of anaemia are seen in about 50–70% at the time of diagnosis. Involvement of the spleen, liver and gastrointestinal tract may occur in about 20–30% of the cases. The unfavourable types of lymphoma may involve the central nervous system.

Management

Lymph node biopsy is done for determination of cellular morphology and immunophenotyping. This is followed by a careful history, physical examination, blood tests, CT and PET for assessment of disease dissemination. The follicular lymphoma is responsive to treatment but is difficult to cure; patients have a median survival of 7–10 years [20]. Treatment outcome has improved with the addition of rituximab to chemotherapy. Two trials have established that rituximab in combination with CHOP chemotherapy is a standard first-line treatment for previously untreated diffuse large B-cell lymphoma at least in the elderly [21]. In the large-cell lymphoma, the event-free survival at 3 years in those less than 65 years is now 80% [22] and 60% in the elderly [23].

Hodgkin's Lymphoma (HL)

HL is a malignant tumour of the lymphatic tissues and weakens the immune system. The age-adjusted incidence rate is 2.7 per 100,000 for men and women per year [24]. The incidence rate for all races is 3.2 and 2.5 per 100,000 for men and women, respectively. The incidence rates are higher in Whites than in Blacks and in Asians [24]. It has a bimodal distribution in people aged 15–25 and a smaller peak after 60 years. More than 70% of HL cases in Asia and South America and 20–40% in the Western world are EBV positive [25]. Other risk factors are genetic susceptibility and environmental factors are occupation, such as woodworkers, and infections such as HIV.

HL is a B-cell lymphoma which is characterised by only about 1% of malignant pathognomonic Hodgkin and Reed-Sternberg (HRS) cells [26]. The Revised European American system classifies HL (REAL) into two main types: classical and nodular lymphocyte predominant [27, 28]. HL has also been classified into classical variant and a nodular lymphocyte-predominant variant characterised by the presence of Hodgkin and Reed-Sternberg cells or lymphocytic and histiocytic cells, respectively, according

to the World Health Organization [29]. The HRS cells attract a supportive microenvironment of immune and stromal cells and suppress local immune reaction thereby promoting its own survival [30]. There is considerable evidence that the Hodgkin and RS cells are tumour cells in classical Hodgkin's lymphoma [30] and are clonal B cells that lost their B-cell phenotype [30]. Immunophenotypical studies have demonstrated lymphoid activation markers including CD15, CD25 and CD30, amongst others [31].

Past infection with Epstein-Barr virus (EBV) is thought to contribute to some cases and has been detected in 40% of cases of classical HL [32], and it is clonal and suggests that the virus may play an important role in the pathogenesis of some types of HL [27, 32].

Symptomatology

Most patients present with cervical and mediastinal adenopathy and may be asymptomatic initially. Symptoms associated with HL include fever, night sweats, weight loss and intense pruritis. Occasionally the fever is periodic (Pel-Ebstein), high fever alternating with periods lasting days to weeks of no fever. Pain may occur in the involved sites with alcohol, but the mechanism is unclear. Pressure on the surrounding structures by enlarged lymph nodes can give rise to various symptoms. Compression of the recurrent laryngeal nerves and the sympathetic gives rise to hoarseness and Horner's syndrome. Pressure of nerve roots cause neuralgic pain, and cough and wheeze can result from tracheobronchial compression. With splenic involvement, splenomegaly results although it is rarely massively enlarged.

Diagnosis and Differential Diagnosis

HL can be definitely diagnosed by lymph node biopsy. HL can mimic other causes of lymphadenopathy such as NHL, leukaemia and infectious mononucleosis amongst others.

Management

1. Tissue biopsy (excision/core biopsy)
2. Staging: history and examination
   Blood tests – liver, renal, etc.
   CT scan for assessment of lymphadenopathy
   Marrow aspirate and trephine
3. Ann Arbor staging of Hodgkin's sans non--Hodgkin's lymphoma
   Stage I: involvement of the single lymph node region only
   Stage II: involvement of two or more regions on the same side of the diaphragm
   Stage III: involvement of lymph nodes and the spleen on both sides of the diaphragm
      i. Above renal vessels – spleen, splenic, hilar, coeliac and portal nodes
      ii. In the lower abdomen– para-aortic, pelvic or inguinal nodes
   Stage IV: extranodal involvement (bone marrow, lung, liver, etc.)
   Early-stage disease, stage I or II; advanced stage, stage III or IV

The early and advanced stages can be further subdivided into favourable and unfavourable. In the case of early-stage unfavourable-unfavourable, features include symptoms (fever, night sweats or weight loss greater than 10% of the body weight in the previous 6 months) or bulky disease individual sites greater than 10 cm in diameter [20]. In the case of advanced-stage, unfavourable features include age>45 years, Stage IV, Hb <105 g/L, WBC >15 × 109, lymphocyte count 0.6 × 109 or 8% of the total WBC and serum albumin <40 g/L [20].

Treatment: cycles of chemotherapy with involved field radiotherapy. Treatment outcome has improved with the addition of rituximab to chemotherapy. Two trials have established that rituximab in combination with CHOP chemotherapy is a standard first-line treatment for

previously untreated diffuse large B-cell lymphoma at least in the elderly [33].

Impact of Haematological Malignancies

The MPN Landmark Survey in the United States demonstrated a remarkable burden of disease across all three MPNs which was not restricted to symptoms but included QoL, productivity and activities of daily living [34]. In about 80% of the patients with multiple myeloma, there are destructive bone lesions giving rise to pain, fractures, mobility problems and neurological deficits and causing disability and morbidity resulting in increases in cost of management [35]. A review of the international literature on the impact of haematological cancers on the quality of life by Allart-Vorelli et al. [36] showed that haematological cancers negatively affected overall QoL in 12 of the 21 studies reviewed, followed by deterioration of physical dimension in 8, psychological QoL component in 11 and social component in 8, and fatigue was the most prevalent physical symptom [36]. In the elderly drug interactions occur due to the presence of comorbidities, and multiple medications and toxicity may increase morbidity and mortality [37]. An important complication of haematological malignancies is bacterial infections, and increasing age is associated with increased mortality [38] (Box 1).

Box 1 Key Points: Lymphoproliferative Disorders

Chronic lymphocytic leukaemia. In about 40–60% 5% of the patients, the lymphocytosis is an incidental finding [7].

Patients may also develop immune-mediated cytopenias such as Coombs positive haemolytic anaemia and immune thrombocytopenia [9–11].

Box 1 Key Points: Lymphoproliferative Disorders (continued)

Antileukaemic therapy is frequently unnecessary in uncomplicated early disease. Stages 0–II may stay alive without treatment for 5–20 years. For Stages III–IV, initial therapy is usually with an alkylating agent such as chlorambucil. Fludarabine is now considered a therapeutic option for initial treatment.

The overall 5-year survival is approximately 60% but depends on the stage of the disease [3].

Non-Hodgkin's lymphoma

The commonest subtypes are the B-cell follicular lymphoma and the diffuse large B-cell lymphoma (DLBCL).

Hodgkin's lymphoma

HL is a B-cell lymphoma. The revised European American system classifies HL (REAL) into two main types: classical and nodular lymphocyte predominant. The classical type includes four subtypes: nodular sclerosing, mixed medullary, lymphocyte depletion and lymphocyte rich lymphoma.

Treatment: cycles of chemotherapy with involved field radiotherapy.

Multiple Choice Questions

1. In chronic lymphatic leukaemia (CLL), the following are true, except:
   A. In 25% of patients, lymphocytosis is an incidental finding.
   B. Splenomegaly is always present.
   C. Coombs positive haemolytic anaemia can occur.
   D. Thrombocytosis is present.
2. In the management of chronic lymphatic leukaemia, the following are true, except:
   A. Oral chlorambucil is extensively used in the elderly.
   B. Patients over the age of 75 years are considered unsuitable for standard therapy.

C. In the elderly with CLL, the presence of comorbidities as well as potential toxicity to therapy needs to be considered.
D. Advanced age and comorbidities are not contraindications for standard therapy.

3. The following are true of Hodgkin's lymphoma, except:
   A. Proportion of EBV-associated cases varies by geographic locale.
   B. Commonly occurs in the 15–35 year age group.
   C. Reed-Sternberg cells are diagnostic feature.
   D. Stage II disease is found on both sides of the diaphragm.
4. The following are true of non-Hodgkin's lymphoma, except:
   A. Majority are T cell rather than B cell in origin.
   B. It is eight times more common than Hodgkin's lymphoma.
   C. Generalised lymphadenopathy may be the first presentation.
   D. The follicular lymphoma is responsive to treatment but is difficult to cure.

MCQ Answers

1 = A; 2 = B; 3 = D; 4 = A

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Part VI

Renal and Lower Urinary Tract Disorders in the Elderly

Structural and functional changes occur with aging which predispose the elderly to a number of renal diseases. Part VI reviews some of the more common kidney diseases, diseases related to the prostate and sexuality in the elderly. The true incidence of glomerular disease in the elderly may be underestimated as a result of fewer biopsies in those above 65 years, especially in those above the age of 75 years. The histopathological change in the elderly include extracapillary proliferation, membranoproliferation, membranous nephropathy, focal-segmental glomerulosclerosis, mesangial glomerulonephritis, minimal change disease, and diabetic glomerulosclerosis. Atherosclerosis causes about 70–90% of renovascular disease (RVD). Several studies have indicated that age is a risk factor for RVD and cause for end-stage renal disease (ERSD). RVDs that cause ESRD are inflammatory vasculitis, nephrosclerosis, RVD atheromatous, and embolic disease. The elderly are susceptible to acute kidney injury (AKI) due to a number of factors such as structural and functional changes due to aging, functional impairment of kidneys secondary to diseases such as hypertension, heart failure and arteriosclerosis, increased susceptibility to nephrotoxins, dehydration and alterations in drug metabolism, and clearance associated with aging. The etiology of AKI is often multifactorial and mortality is higher in the elderly. Chronic kidney (CKD) disease is a significant problem in the elderly and is associated with a high risk of renal failure and death. It is a progressive disease. Hypertension, intraglomerular pressure, proteinuria, and renal damage are interrelated in the background of CKD progression. Benign prostate hypertrophy (BPH) is a common part of aging, and by the age of 80 years about 90% of the men will have histological evidence of BPH. Carcinoma of the prostate is the commonest known cancer affecting 30% of men at the age of 50 and 90% at the age of 90 years. There is a worldwide increase in erectile dysfunction (ED), and the prevalence increases with age.

Glomerular Disease in the Elderly

30

Contents

Abstract

This is a brief review of glomerular disease in the elderly. The incidence of glomerula disease (GD) in the elderly is relatively higher than in young adults. This has been attributed to the increase in malignancies and in the use of a variety of drugs. The histopathological change in the elderly includes extracapillary proliferation, membranoproliferation, membranous nephropathy, focal-segmental glomerulosclerosis, mesangial glomerulonephritis, minimal change disease and diabetic glomerulosclerosis. In the elderly, postinfectious GN may account for a higher proportion in the elderly.

Keywords

Glomerular disease · Postinfectious glomerulonephritis · Amyloidosis · Multiple myeloma

Introduction

The true incidence of glomerular disease in the elderly may be underestimated due to fewer biopsies in those above 65 years, especially in those above the age of 75 years [1]. The incidence of glomerular disease (GD) in the elderly is relatively higher than in young adults [2]. This has been attributed to the increase in malignancies and in the use of a variety of drugs. It is likely that any apparent difference reflects the type of clinical practice rather than any inherent difference in the aged kidney [3]. In a retrospective study of glomerular disease in the elderly, the histopathological changes included extracapillary proliferation, membranoproliferation, membranous nephropathy, focal-segmental glomerulosclerosis, mesangiangial gomerulonepharitis, minimal change disease and diabetic glomerulosclerosis [4]. In elderly patients glomerular disease may be primary or secondary to system disease in the ratio 7.3 [5].

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_30

Clinical Manifestations

Nephritic Syndrome

Nephritic syndrome can result from primary renal disease due to post-streptococcal GN, lupus nephritis, antiglomerular basement membranous disease, IgA nephritis, anti-neutrophil cytoplasmic antibody (ANCA) small vessel disease [6], membrane proliferative glomerular nephritis and mesangial proliferative GN. In patients with asymptomatic urinary abnormalities, IgA nephropathy is the most frequent glomerulonephritis at any age [7]. Nephritic syndrome is characterized by hypertension, red blood cell casts, mild proteinuria (1–2 g/24 h), oedema of acute onset and renal functional impairment. Pauci-immune crescentic glomerulonephritis is the most common type of glomerular nephritis (GN) in the elderly [8, 9]. It can present as a vasculitis and about 80% of the patients have a positive serum ANCA, and the two common lesions are Wegener's granulomatosis (mostly C-ANCA) and microscopic polyarteritis nodosa (mostly P-ANCA) [10]. Renal biopsy is strongly recommended for its diagnosis in the elderly. Without treatment it has an unfavourable outcome [9].

In India, endocapillary proliferative GN of the postinfectious aetiology accounted for 82% of the acute GN elderly patients and nearly 40% of them required dialysis [5]. In the elderly, post-streptococcal glomerulonephritis is uncommon, and a recent review of post-streptococcal GN patients, mean age 64 years, stated that 38% of patients had an underlying disorder associated with immunocompromise [11]. Postinfectious glomerulonephritis may be associated with organisms other that streptococcus, and given the greater frequency of other infections in the elderly, postinfectious GN may account for a higher proportion in the elderly [12]. In the elderly, acute postinfectious glomerulonephritis is often associated with renal failure [13], and crescentic glomerulonephritis has an unpromising prognosis [13].

Nephrotic Syndrome

Nephrotic syndrome is a complex clinical picture characterized by massive proteinuria (>3.0 g/24 h), hypoalbuminaemia, hyperlipidaemia and generalized oedema [14]. Nephrotic syndrome can result from primary or secondary renal disease. The most frequent is membranous nephropathy (28–35%) [7, 14, 15]. Minimal change disease is seen in about 11–16% of patients [14, 15]. Nephrotic syndrome may be associated with other systemic diseases such as primary amyloidosis [15], multiple myeloma, diabetes and systemic lupus erythematosus, among others. In a study of 85 patients with primary renal disease, 61 patients presented with idiopathic nephrotic syndrome. Compared with the young, in the elderly, membranous nephropathy, crescentic GN, membranoproliferative GN, amyloidosis, light chain disease and thrombotic thrombocytopenic purpura were more prevalent, but IgA nephropathy and lupus nephritis were less common [16].

Minimal change disease (MCD) and membranous nephropathy (membranous glomerular nephritis) are the two common causes of this syndrome in the elderly [15]. MCD could account for 15–20% of patients with nephrotic syndrome [14, 15, 17, 18]. Minimal change disease is relatively a benign disease, and in the elderly, however, it is often accompanied by acute renal failure. It is often associated with lymphoproliferative disorders. Non-steroidal anti-inflammatory drugs are emerging as an important cause of minimal change disease in the elderly [8]. It responds to corticosteroids and/or cyclophosphamide, but if untreated and in those who do not respond, the disease may progress to end-stage renal disease [13].

Membranous nephropathy is often associated with cancer of the lung, colon and possibly lymphomas, and available data is suggestive that an extensive search for a tumour is unnecessary [8]. After the age of 60 years, amyloidosis and multiple myeloma make up 15–20% of nephrotic syndrome in the elderly [12]. Focal glomerulosclerosis may follow an aggressive clinical course

in the elderly [13]. Prognosis depends on the cause. An older adult presenting with renal insufficiency, hypercalcaemia and an elevated total protein level must be evaluated for multiple myeloma [8]. IgA nephropathy, primary amyloidosis or related light chain deposition disease may account for one-fifth of the patients over the age of 60. The outcome of membranous nephropathy in the elderly is similar to that in younger patients [13].

Impact

With age renal function declines even in the absence of renal disease; furthermore, in the elderly, comorbid conditions confound renal function [19]. Pauci-immune, ANCA-positive and crescentic GN are the most common types of glomerular disease in the elderly [8, 9]. Glomerular disease if left untreated in the elderly rapidly leads to end-stage kidney disease [12]. The same primary glomerular disease diagnosed on pathologic evidence may behave differently in patients, from benign to severe [20]. The clinical characteristics of the different subtypes may be different [13], and their response to treatment varies. Pauci-immune, ANCA-positive and crescentic GN if untreated have a poor prognosis [8, 9, 13]. The prognosis in acute postinfectious GN is poor, and it is often associated with renal failure in older patients [13] (Box 1).

Box 1 Key Points: Glomerular Disease

- Glomerular disease can present in a variety of ways, nephritic syndrome and nephrotic syndrome, may also present as hypertension, asymptomatic urine changes and chronic kidney disease.
- Pauci-immune, ANCA-positive and crescentic GN are the most common types of GN in the elderly [8, 9], and the outcome is poor if untreated [8, 9].
- In the elderly, post-streptococcal glomerulonephritis is uncommon [11].

Box 1 Key Points: Glomerular Disease (continued)

- Postinfectious glomerulonephritis may be associated with organisms other than streptococcus and is given the greater frequency of other infections in the elderly [12].
- Postinfectious GN may account for a higher proportion in the elderly [12].
- After the age of 60 years, amyloidosis and multiple myeloma make up 15–20% of nephrotic syndrome in the elderly [12].

Multiple Choice Questions

1. The following glomerular diseases commonly occur in the elderly, except:
   A. Pauci-immune, MPO-ANCA-positive and crescentic glomerular nephritis.
   B. Post-streptococcal glomerulonephritis.
   C. Ten to 20% of older individuals have lupus nephritis.
   D. Ten to 20% of individuals with nephrotic syndrome have minimal change disease (MCD).

MCQ Answers

1 = B

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Renovascular Disease in the Elderly 31

Contents

Abstract

Renovascular diseases (RVDs) that cause end-stage renal disease (ESRD) are inflammatory vasculitis, nephrosclerosis, RVD atheromatous and embolic disease. Renal artery stenosis is the cause of renovascular hypertension in at least 90%. Atherosclerosis involves 80% of the ostium and the proximal one-third of the renal artery. Renovascular hypertension and ischaemic nephropathy are most commonly seen in patients with atherosclerotic renal artery stenosis. Surgical procedures include PTRA and PTRAS (percutaneous renal artery angioplasty and stenting). This review summarises and provides an update in the management of renovascular disease.

Keywords

Renovascular disease · Renovascular hypertension · Ischaemic nephropathy · Atherosclerotic renal artery stenosis

Introduction

Renovascular disease (RVD) is a progressive condition that causes narrowing or blockage of the renal arteries or veins resulting in reduced renal perfusion [1]. RVD and nephrosclerosis are the most prevalent. RVDs that cause end-stage renal disease (ESRD) are inflammatory vasculitis, nephrosclerosis, RVD atheromatous and embolic disease. Renal artery stenosis is the cause of renovascular hypertension in at least 90%.

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_35

Atherosclerosis causes about 70–90% of RVD. Atherosclerosis involves 80% of the ostium [2] and the proximal one-third of the renal artery. Renovascular hypertension and ischaemic nephropathy are most commonly seen in patients with atherosclerotic renal artery stenosis [3]. It is commonly associated with other microvascular diseases including nephrosclerosis and diabetic nephropathy [4, 5]. High-grade ARVDs are associated with extra renal vascular disease such as carotid and lower-extremity arterial disease [4, 6]. One-third of the patients with heart failure exhibit ARVD [7].

Clinical Presentation

Patients with ARVD have a varied presentation. Many patients with renal artery stenosis are asymptomatic. Severe hypertension, hypertension which is often refractory and not responding to three or more blood pressure medications, hypertension of sudden onset in an elderly after the age of 55 years, progressive renal dysfunction and rise in the serum creatinine with ACE inhibitors, unexplained renal unilateral atrophy and atherosclerotic disease elsewhere may be indicative of atherosclerotic renovascular disease. Recurring pulmonary oedema or sudden unexplained pulmonary oedema is a complication of bilateral renal artery stenosis [8, 9]. Other clinical signs associated with RVD are abdominal bruit. Atheroembolic renal disease may present with abdominal pain, confusion, skin lesions such as purpura and renal failure (Box 1).

Box 1 Manifestations of Renal Vascular Disease (RVD)

Abdominal bruit
Atherosclerotic disease elsewhere
Smoking
Late-onset hypertension (renal artery stenosis)
Renal failure with ACE inhibitors
Positive results with captopril test
Sudden and recurrent pulmonary oedema

Information sources: Pickering et al. [8] and Walker et al. [9]

Diagnosis

Selected investigations will be indicated to confirm and evaluate the specific condition. In the elderly, a major consideration is whether to investigate or not, because intervention is a problematic risk of making the patient worse. There is a high presence of renal artery stenosis even in the absence of the usual clues in patients with atherosclerosis elsewhere [4]. Ultrasonography is non-invasive and is often the first line in the investigation of a patient with suspected renovascular hypertension. The diagnosis of renal artery stenosis by ultrasound is based on the assessment of velocities and waveform traces but is insensitive to stenosis less than 50% and the ability to differentiate occlusion from severe stenosis [10]. Captopril scintigraphy is frequently used in patients with renovascular hypertension who are not uraemic and is shown to be effective in the diagnosis and helps to predict blood pressure lowering outcome after intervention [11]. Contrast-enhanced computerised tomography angiography (CE-CTA), contrast-enhanced magnetic resonance angiography (CE-MRA) and spiral computed tomography [12] are more superior to ultrasonography for the detection of renal artery stenosis. There is a known risk of contrast in the elderly with impaired GFR. Prediction rules may help to select patients for angiography [13]. One could predict whether the renal tissue is viable and revascularisation is beneficial by measurement of the kidney size, GFR of each kidney and renal biopsy [10] (Box 2).

Box 2 Diagnostic Tests in RVD Duplex Ultrasound Sonography

CT angiography

MR angiography

Catheter angiography in those with high clinical index of suspicion and inconclusive non-invasive tests

Skin biopsy

Muscle biopsy

Renal biopsy rarely performed in elderly

Treatment

Medical

In patients with ARAS, elevation of serum creatinine can result from excessive lowering of the blood pressure; however, several studies have shown that tight blood pressure controls have led to better outcomes [14, 15]. Unstable atherosclerotic plaques can embolise, and statins can not only cause plaque regression but also have a specific role in its management [16].

Surgical

Surgical procedures include PTRA and PTRAS (percutaneous renal artery angioplasty and stenting). Patients with severe hypertension resistant to medical therapy, recurrent flash pulmonary oedema, rapidly progressive renal failure due to ARAS [17, 18], bilateral renal artery stenosis or stenosis to a single functioning kidney and ERSD [17] and those with reversible azotaemia during ACEi or ARB therapy [17] should be offered revascularisation. Randomised controlled trials in patients with renal hypertension have shown no clear benefit of adequate revascularisation over medical therapy [2]. However, the renal artery stenting in ARAS was more encouraging [2]. The GREAT trial comparing drug-eluting stent (DES) to bare metal low-profile tent found a relative reduction of 50% in the angiographic binary renal artery in-stent restenosis [19]. Current evidence suggests that patients with bilateral RAS or unilateral functioning RAS and a subset of patients with resistance index <80% at the level of the segmental arteries may benefit from PTRA or PTRAS in case of renal artery stenosis [21]. Embolic protection devices are used to prevent distal embolisation to prevent worsening of renal function after stenting. The RESIST trial has demonstrated no overall benefit [20].

Impact

ARVD is a cause of chronic kidney disease (CKD) and end-stage renal disease (ERSD) which increase with age. It is commonly associated with other microvascular diseases including nephrosclerosis, diabetic nephropathy [4, 5] and extra renal vascular disease such as carotid and lower-extremity arterial disease [4, 6]. One-third of the patients with heart failure exhibit ARVD [7]. Persons older than 70 years with CKD are at the double risk for physical impairment, frailty and cognitive dysfunction [21]. Patients with advanced CKD often have severe psychological disorder, and about 25% of patients on haemodialysis have clinical depression, which is associated with low quality of life and increased mortality [22] (Box 3).

Box 3 Key Points. Renovascular Disease

- Atherosclerotic renal artery stenosis is the cause of renovascular hypertension in at least 90% of the patients.
- Patients with ARVD have varied presentation.
- Contrast-enhanced computerised tomography angiography (CE-CTA) and contrast-enhanced magnetic resonance angiography (CE-MRA) [12] are more superior to ultrasonography for the detection of renal artery stenosis.
- In patients with ARAS, elevation of serum creatinine can result from excessive lowering of the blood pressure; however, several studies have shown that tight blood pressure controls have led to better outcomes [14, 15].
- Current evidence suggests that patients with bilateral RAS or unilateral functioning RAS and a subset of patients with resistance index <80% at the level of the segmental arteries may benefit from PTRA or PTRAS in case of renal artery stenosis [3].

Multiple Choice Questions

1. The following are true with renal artery stenosis, *except*:
   A. May present as sudden unexplained pulmonary oedema.
   B. ACEi and ARBs can cause renal failure in patients with renal artery stenosis.

C. Seventy-five percent of renal artery stenosis is due to fibromuscular dysplasia.
D. Renal artery stenosis is the cause of renovascular hypertension in at least 90% and atherosclerotic renal artery stenosis is a disease of the elderly.

MCQ Answers

1 = B

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Acute Kidney Injury

32

Contents

Abstract

The term acute kidney injury (AKI) had been proposed to embrace the entire spectrum of syndrome from minimal changes in renal function to the need for renal replacement therapy (RRT). The elderly are susceptible to AKI due to a number of factors such as structural and functional changes due to ageing; functional impairment of kidneys secondary to diseases such as hypertension, heart failure and arteriosclerosis, increased susceptibility to nephrotoxins, dehydration and alterations in drug metabolism and clearance associated with ageing. The prognosis is dependent on a number of factors such as type, cause, severity, other disease processes among others. The review provides an overview of acute kidney injury, prevalence and mechanisms followed by clinical management.

Keywords

Acute kidney injury · RIFLE classification · Nephrotoxins · Dehydration · Renal replacement therapy · Acute tubular necrosis

Introduction

The term AKI had been proposed to embrace the entire spectrum of syndrome from minimal changes in renal function to the need for renal replacement therapy (RRT) [1]. The RIFLE classification (Table 1) provides a graded definition of AKI based on physical measurement of serum creatinine or glomerular function rate (GFR) or urine output [2] and embraces the entire spectrum from minor change in renal function to renal replacement therapy [3]. It has been validated in numerous studies [3]. The Acute Kidney Injury

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_33

Network (AKIN) is a modification of RIFLE criteria and requires an absolute serum creatinine of 0.3 mg/l in a 48 h period for the diagnosis of AKI [4] (Fig. 1).

AKI is known to affect 1–20% of intensive care unit patients [5] depending on the definition used. Using the RIFLE classification, AKI was found in 9%, 5%, 4% of hospital admissions respectively and an approximate 17%, 12% and 7% of critical care admissions [2]. Males and females are equally affected. Acute renal failure is quite common in the elderly [8–11] and patients over the age of 70 years are at high risk for developing AKI [12]. The incidence of AKI patients in the ICU is increasing, 1–25% of ICU patients are reported to have AKI [7]. AKI patient in ICU have a longer stay in hospital [3]. In the ICU setting the prevalence of severe AKI requiring some form of renal replacement therapy (RRT) approached 6% and an inpatient mortality rate of 60.3% [13]. Fifty to 60% of ICU patients with AKI who are treated with some form of RRT die and of the surviving patients 5–20% remained dialysis dependent at time of discharge [3]. The elderly are susceptible to AKI due to a number of factors such as structural and functional changes due to ageing [9, 11]; functional impairment of kidneys secondary to diseases such as hypertension, heart failure and arteriosclerosis [9], increased susceptibility to nephrotoxins [14, 15] dehydration [12, 14] and alterations in drug metabolism and clearance associated with ageing [15]. Mortality is higher in the elderly with AKI [12].

Table 1 RIFLE classification

Category	GFR criteria	Urine output criteria
Risk	Increased creatinine X1.5 or GFR decrease >25%	<0.5 ml/kghX6hr
Injury	Increased creatinine X 2 or GFR decrease >50%	<0.5 ml/kgh X 12 hr
Failure	Increased creatinine X3.0 or GFR decrease >75%	<0.3 ml/kghX24 hr. or Anuria X 12 h
Loss	Persistent ARF = complete loss of renal function >4 weeks	
ESKD	End stage kidney disease (>3 months)	

Information sources: Bellomo et al. [5, 6]

ARF comprises three main categories, pre-renal, renal and post-renal. Three important factors in the pathogenesis of pre-renal ARF are volume depletion, decreased effective blood volume and haemodynamic. With ageing there is an impairment in the ability to concentrate urine and conserve sodium and water. These physiological changes in the elderly make them prone to the risk of volume depletion and the pre-renal type of ARF. In pre-renal type, the kidneys are structurally normal and the impairment of renal function is due to reduced blood flow (RBF). Reduction in RBF results in lowering of the glomerular

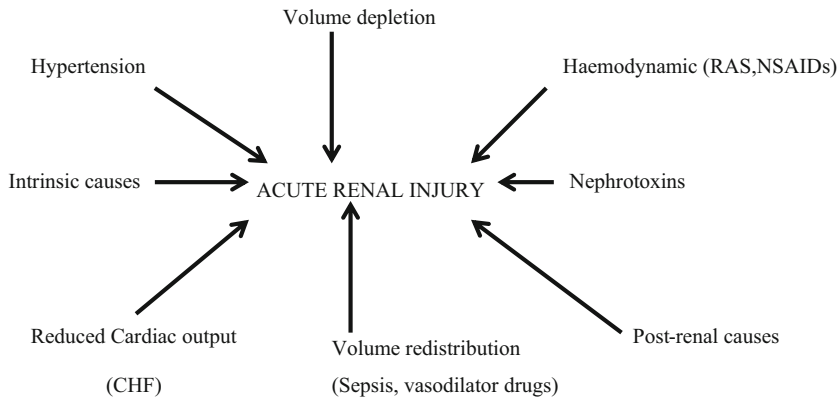

Fig. 1 The aetiology of Acute kidney injury. Informations sources: [12, 22, 29, 30]

filtration pressure and decrease in glomerular filtration rate (GFR) regardless of the cause. The GFR and RBF in conditions such as in real or effective hypovolaemia are particularly sensitive to autoregulatory mechanisms. In the elderly there is a derangement in autoregulatory defense mechanisms which, in combination with volume depletion can lead to ischaemia and AKI [16]. Activation of the renin-angiotensin-aldosterone axis, stimulation of vasopressin secretion and enhanced regulation of the sympathetic system are the normal adaptive responses to volume depletion [17]. Andreucci et al. [18] used the term 'vasomotor nephropathy' to define ARF due to an ischaemic insult and is associated with retention of nitrogenous waste in the body following haemorrhage, severe salt depletion, burns, shock, sepsis, trauma, rhabdomyolosis, haemolytic reactions or congestive heart failure.

Vasoconstrictive hormones released as a response to systemic hypotension may have a direct effect on glomerular permeability. There is constriction of the renal afferent arterioles due to increased plasma adrenaline and stimulation of the sympathetic nerves. During the period of reduced RBF the kidneys are vulnerable to other insults. Drugs such as NSAIDs and ACEIs can alter intrarenal hemodynamics in the elderly particularly when associated with salt depletion and hypovolaemia [18] and are susceptible to the combined effects of nephrotoxic drugs such as aminoglycosides or contrast agents and pre-existing volume depletion [19]. NSAID-induced ARF may be caused by acute interstitial nephritis [20] or haemodynamically – mediated and the former perhaps and the latter is directly related to the reduction of prostaglandin synthesis [21]. By relaxing the preglomerular resistance the vasodilator protaglandins preserve renal blood flow and glomerular filtration rate and antagonise the vasoconstrictive action of angiotensin II ad norepinephrine [21]. The increased renal susceptibility to toxic substances in the elderly is due to an imbalance between vasoconstrictor and vasodilator factors, resulting in a greater tendency to vasoconstriction together with increased levels of oxidatively modified molecules which make them more prone to toxic injury [15].

The pathophysiology in renal or intrinsic category will depend on the specific cause and there are a variety of causes. There are two significant factors in its pathogenesis, namely ischaemia and nephrotoxins. Acute glomerulonephritis (AGN), rapidly progressive glomerulonephritis (RPGN) and vasculitis give rise to accumulation of inflammatory cells in the glomeruli resulting in reduce glomerular filtration. In interstitial nephritis the inflammatory reaction is confined to the interstitium. Drugs, infiltrative disease and infectious pyelonephritis are common causes of interstitial nephritis. Acute tubular necrosis (ATN) is the most important cause of intrinsic ARF [22] and is often initiated by acute injury to the proximal tubular epithelial cells by acute ischaemic or nephrotoxic events [23]. Apart from alteration of autoregulation the ageing tubular cells are more susceptible to ischaemic damage due to decline in the cellular antioxidant defences [24]. Detachment of the tubular epithelial cells from the basement membrane and the back-leak of the glomerular filtrate cause tubular obstruction resulting in decline in GFR [25]. The pathogenesis of ATN involves interaction of a number of processes that include endothelial injury, microvascular flow disruption, tubular hypoxia, tubular obstruction and apotosis [22]. In response to the tubular cell injury there is profound secondary vasoconstriction which is the predominant mechanism [23] and it is the imbalance between vasoconstrictive and vasodilator mediators and vascular obstruction caused by cell aggregation that are involved in the pathophysiology of AKI [25]. Creatinine clearance has both filtration and secretory components [26]. Slight changes in the plasma flow-dependent component of active creatinine secretion by the organic ion transport systems in the proximal tubule may be indicated by moderate changes in the serum creatinine [27] and can be seen as a biomarker for acute tubular injury [28] . Disease of the renal arteries leads to ischaemia of the kidneys resulting in reduced renal function. In the post-renal type as the back pressure increases the GFR becomes reduced. Furthermore the increased tubular pressure leads to decreased RBF due to reflex vasoconstriction of the afferent arterioles.

The aetiology of AKI (32.1) is often multifactorial [8, 12]. In the elderly pre-renal type accounts for about one-third of hospital cases with AKI and in over 50% of the hospitalized patients it is intrinsic or renal [22]. Post-renal causes increases with age. In a study of 437 patients with AKI 35% were above the age of 70 years and the prevalence of AKI was 3.5 times higher in the elderly compared to younger people [12].

Pre-renal type; Hypovolaemia results from reduced fluid intake or increased loss for example diarrhoea and vomiting, blood loss, diuretics, and skin losses (burns). Although in many the renal hypoperfusion can be reversed with adequate fluid replacement some may progress to ATN and this is more frequent in the elderly [29]. Dehydration was the most frequent cause of prerenal AKI in the elderly (1%) [12]. Other causes being reduced cardiac output from congestive heart failure, volume redistribution as in peripheral vasodilatation following sepsis, vasodilator drugs and anaphylaxis, and altered vascular resistance following the use of drugs such as NSAIDs, cyclosporine, ACE inhibitors and in diseases like liver disease. The elderly are exposed to increased risk of dehydration due to tubular function changes [30].

Renal or intrinsic causes can be due to abnormalities in the glomerulus (acute glomerulonephritis), tubules (acute tubular necrosis), interstitum (acute interstitial nephritis) and in the vasculature (vasculitis and the last should not be missed as it is potentially life threatening [22]. ATN is the most common cause of intrinsic AKI and is the cause in 50% of hospitalized patients and up to 76% of the patients in intensive care units [22]. ATN was diagnosed in 40% of elderly patients with AKI compared to 52% in the younger individuals [12]. AKI is commonly iatrogenic and common iatrogenic combinations include non-stroidal anti-inflamatory drugs (NSAIDs) and renal artery stenosis, hypertension or congestive heart failure, angiotensin-converting enzymes (ACE) and diuretics and small and large vessel renal artery disease; pre-existing renal disease and radiocontrast agents, aminoglycosides or cardiovascular surgery; hypovolaemia and radiocontrast agents, heme pigments and aminoglycosides [2, 22].

Post-renal causes include obstructon at the level of the pelvis and ureter (stones, malignancy, inflammation), bladder (benign prostrate hypertrophy, cancer of the prostate and bladder, stones) and the urethra (strictures). Bladder outlet caused by benign prostatic hypertrophy is a common cause of ARF in the elderly.

Symptoms

There is a decrease in the amount of urine passed with complaints of lethargy, fatigue and swelling of the face, feet and hands There is nausea and vomiting, abdominal pain and diarrhoea. There is mental confusion together with inability to concentrate. Volume loss may occur from vomiting, diarrhoea, polyuria, excessive sweating or haemorrhage in the pre-renal type.

Diagnosis

A preliminary diagnosis of AKI is made from a good history and previous data of renal function. The history should include a family history of renal disease, allergies, present and past medications, recent radiological procedures, surgery, chronic renal disease and history of voiding problems.

The distinction between acute and chronic may not be clear especially in patients presenting with uraemia. It is not uncommon for patients with chronic renal failure to present with superimposed acute-on-chronic renal failure and it is important to exclude chronic renal failure. Patients with chronic renal failure have a history of chronic renal disease and laboratory investigation may show a normocytic normochromic anaemia and high serum phosphate. Ultrasonography may reveal bilaterally small kidneys.

It is important to determine whether AKI is of the pre-renal type or post-renal type for both are potentially reversible [20]. It is essential that

ultrasonography is done since there is a high incidence of obstructive causes for AKI in the elderly. In the case of the latter there may be a history of stones or symptoms of prostatic obstruction namely frequency, urgency and hesistancy. Early identification with renal imaging, ultrasound to assess kidney size and to exclude urinary obstruction is essential.

A thorough physical examination with particular attention to decreased skin turgor, dry mucous membranes, weight loss, and orthostasis (pulse rate and blood pressure recorded in the standing and recumbent positions) suggesting hypovolaemia. The history, physical examination and urinanlysis are usually sufficient to rule out pre-renal and post-renal causes.

Acute glomerulonephritis (AGN) or rapidly progressive glomerulonephritis (RPGN) should be suspected when there is a massive proteinuria [20]. AGN is an uncommon cause of ARF but when fulminant it is associated with active urinary sediment. RPGN and glomerular nephritis associated with endocarditis are the most common glomerular diseases to cause sudden renal deterioration. Serological tests (C3, ANCA, ANA, AdsDNA etc.) may help in differentiating acute glomerulonephritis from the various causes of vasculitis.

In pre-renal ARF in response to the acute reduction of RBF and GFR there is avid resorption of filtered salt and water so that there is a small amount of concentrated and NaCl-poor urine excreted. Fractional excretion of sodium (FENa), urine-plasma creatinine ratio and urinary and sodium osmolality are reliable indices that discriminate between 'tubular' and 'non-tubular' disorders [31]. Fractional excretion of Na and urine osmolality may be measured but the widespread use of diurtetics in the elderly gives rise to unreliable results [22, 25]. Evaluation of the urine chemistries and urine sediment may help to differentiate between renal vasoconstriction with intact tubular function (prerenal azotaemia) and established ARF [32]. The finding of red blood cell cast in the urine indicates glomerular pathology and calls for a renal biopsy. Pigmented granular casts are indicative of tubular damage. The causes of pre-renal AKI are shown in Box 1.

Box 1 Causes of Pre-renal AKI

Volume depletion: diarrhoea, vomiting, sweating, blood loss, skin losses, renal loss (diuretics)

Decreased effective arterial blood volume: systemic vasodilatation peripheral (sepsis, anaphylaxis, vasodilators), congestive heart failure, liver failure

Haemodynamic: renal artery stenosis, NSAIDs

Information sources: Andrecucci et al. [18].

A history of exposure to nephrotoxins and any recent radiological examination should raise the suspicion of ATN. Allergic interstitial nephritis is suspected if the patient presents with fever, rash, arthralgias or exposure to certain medications such as NSAIDs and antibiotics [2]. Antibiotics especially semi-synthetic penicillins commonly give rise to ATN and is associated with blood eosinophilia and eosinophiluria [20]. Pigment induced ARF occurs with rhabdomyolysis and the common causes are alcoholism, trauma, exertional heatstroke, HIV infection and hydroxymethylglutaryl coenzyme reductase inhibitors. Acute intrinsic renal failure can follow renal arterial or venous occlusive processes. The clinical presentation is the typical triad of severe or sudden lower back pain, severe oliguria and macroscopic haematuria.

The diagnosis of AKI rests on the serum creatinine which is aim perfect marker of GFR .The treatment of and prevention of AKI in the future will depend on the early detection of kidney injury. Studies in AKI pathophysiology has led to the identification a number of biomarkers cystatin C [33], KIM-1 [34] and neutrophil geletinase associated lipocalin (NGAL) [35] of early kidney injury are being intensively investigated [28]. The best studied alternative to serum

creatinine as a marker of GFR is cystatin C [36] and may be superior to serum creatinine for the early detection of kidney injury [33, 37]. The levels of Cystatin C are influenced by high doses of corticosteroids and hyperthyroidism causing an increase and hypothyroidism a decrease in the levels [36]. It has been reported that the pro-atrial natriuretic peptide (1–98) was superior to cystatin C for prediction of AKI [38]. Another method which is a rapid, reproducible technique to measure total or individual kidney GFR is by measuring external whole-tissue radioactivity after intravenous injection of Technetium-labelled diethylenetriaminepentaacetic acid [39].

Clinical Course and Prognosis

The clinical course is to a large extent dependent on the underlying cause. The commonest cause in the intrinsic type of ARF is acute tubular necrosis. The clinical course of ATN is variable depending on the severity and duration of the renal insult. It may last for 6 weeks even after relatively short-lived initial insult. The clinical course is characterised by three sequential phases, oliguric, maintenance followed by diuresis and recovery. During the oliguric phase there is rapid deterioration of renal function stabilizing to the maintenance phase. This phase can last 1–2 weeks or be prolonged for several months. During recovery phase the patient may experience polyuria with significant diuresis. The patient's renal function gradually recovers with normalization of urine ouput and a fall in the serum creatinine.

Despite the advances in critical care medicine and renal replacement therapy (RRT) the current mortality rates are close to 75% [22]. Patients with AKI who are treated with RRT still have a mortality of 50–60% and amongst survivors 5–20% are dependent on dialysis at the time of hospital discharge [3]. In one study the overall mortality in the elderly hospitalized patients was 12.7% while elderly with ARF it was 25.4% [40] and in another study it was upto 50% [41].

The prognosis is dependent on a number of factors such as type, cause, severity, other disease processes among others. Prerenal and postrenal if diagnosed and treated early often return to normal or near normal renal function. In community acquired ARF patients secondary to volume depletion it is estimated that as much as 98% is potentially reversible. Non-oliguric ARF (>400 ml/days) has generally lower mortality compared to oliguric ARF (<400 ml/days) and this reflects that the former is usually caused by drug-induced nephrotoxicity and interstitial nephritis and have few other systemic complications [2]. Patients with ATN and RPGN may not recover or may only partially recover their renal function [20]. Sepsis, oliguria and hypotension are independent predictors of poor outcome [40]. With the advent of dialysis the most common cause of death associated with ARF are sepsis, cardiac failure and pulmonary failure [2].

ARF has been reported to affect 1–25% of intensive care unit patients depending on the definition and has led to mortality rates ranging from 15–60% [7]. There seems to be a step-wise relationship between RIFLE categories of renal injury and mortality. Compared to non-AKI the relative of death for Risk is 2.4, Injury 4.15 and Failure 6.5 [2]. The prospect for renal recovery of kidney function after AKI in the elderly is less likely [42].

Management

The treatment of pre-renal and ATN is mainly supportive [22], treatment of the underlying cause and RRT are the main options. Any reversible cause should be identified and treated for example, volume depletion, withdrawal of toxic medications or relieve of obstruction. Underlying disease processes such as shock, sepsis, acute pancreatitis and hypercalcaemia which initiated the AKI may cause death of the patient rather than the complications [43] In patients with vasomotor shock with AKI, vasopressors are used commonly in association with the fluids [44]. Haemodialysis and nutritional support are common measures for patients with ATN [20]. It is justifiable to treat RPGN with corticosteroids

and immunosuppressive therapies. In addition haemodiafiltration instead of haemodialysis can be used in patients who are haemodynamically unstable with persistent low blood pressure [20].

Further measures include treatment of life-threatening complications such as hyperkalaemia, pulmonary oedema, metabolic acidosis, sepsis, respiratory failure and shock [22]. Sodium polystyrene sulphonate is sometimes given by mouth or rectally to treat hypekalaemia. Acute life threatening hyperkalaemia is an indication for intermittent haemodialysis because of the higher efficacy of dialysis in the clearance of low molecular weight substances [25]. Calcium salts (calcium carbonate) or sevelamer may be given to prevent or treat a high level of phosphorus in the blood. Moderate or severe acidosis may require treatment with sodium bicarbonate. Haemodiafiltration has been shown to improve acid-base balance and uraemia better than the standard haemodoalysis [20].

Most patients with AKI are volume depleted at the beginning or have some degree of volume depletion and fluid therapy should be used based on clinical assessment. Even though volume depletion can be detected by physical examination it can be subtle especially when fluid loss has occurred quickly and recently [43] Fluid intake is usually restricted to replacing the amount lost from the body.

Impact

AKI is a common complication in hospitalised patients [44–46] and is associated with increased morbidity and mortality [46–49] and poor outcomes in the elderly [50–52]. Nine percent of all admissions and 15% non-maternity and non-day case admissions to hospital had an episode of AKI with increased short an long term morbidity and mortality [53]. The mortality of severe AKI requiring intensive care is high [54]. There is increased risk of long-term morbidities [44] including chronic kidney disease (GKD) and accelerated progression to end stage kidney disease (ESRD) [55]. The risk of ESRD in hospitalised elderly patients with AKI was 13 times higher than compared to those without AKI [56]. Because of the higher prevalence of systemic diseases such as hypertension, diabetes, heart failure, cardiovascular and peripheral vascular disease among others, the elderly have a greater tendency to develop AKI [17].

Patients with AKI are associated with increased utilization of health resources and health care costs [46, 57] and negative long-term outcomes [46]. Apart from high mortality, treatment with renal replacement therapy (RRT) is costly [58]. Two-hundred seventeen patients with AKI admitted to the ICU and 143 after ICU admission were studied [54]. Renal replacement therapy was used in 174 patients and 58% died during hospital stay [54]. In another study only 55% with AKI had complete recovery among those admitted to ICU [59].

Kerr et al. [46] estimated the annual cost of AKI – related in-patient care in England to be pounds 1.02 billion just over 1% of the NHS budget. Furthermore they reported that if 20% of AKI cases could be prevented there would be a gross savings in the region of pounds 200 million a year [46] (Box 2).

Box 2 Key Points: Acute Kidney Injury (AKI)

The aetiology of AKI is often multifactorial [8, 12].

In the elderly pre-renal type accounts for about one-third of hospital cases with AKI and in over 50% of the hospitalized patients it is intrinsic or renal [22].

Post-renal causes increases with age.

It is important to determine whether AKI is of the pre-renal type or post-renal type for both are potentially reversible [20].

The distinction between acute and chronic may not be clear especially in patients presenting with uraemia.

It is essential that renal ultrasonography is done since there is a high incidence of obstructive causes for AKI in the elderly.

(*continued*)

Box 2 Key Points: Acute Kidney Injury (AKI) (continued)

Microscopic examination of the urine will help to distinguish glomerular from tubular damage.

The treatment of pre renal and ATN is mainly supportive [22], avoidance of nephrotoxic substances, treatment of the underlying cause and RRT.

Multiple Choice Questions

1. The following causes of acute kidney injury (AKI) are true EXCEPT:
   A. Volume depletion from vomiting, diarrhoea.
   B. Acute tubular necrosis (ATN) is not at common cause of in the elderly
   C. The use of ACE inhibitors in patients with small and large vessel renal arterial disease.
   D. Postrenal obstructive causes increase with age and are important.
2. The distinction between acute and chronic kidney disease may not be clear. Which of the following suggest chronic rather than acute.
   A. History of chronic kidney disease.
   B. Presence of normocytic normochromic anaemia.
   C. Low serum phosphatase.
   D. Ultrasound may reveal bilaterally small kidneys,
3. The following in relation to Acute Kidney Injury (AKI) are true EXCEPT:
   A. Fifty to 60% of patients with AKI treated with some form of RRT die.
   B. Acute tubular necrosis (ATN) is the result of acute injury to the distal renal tubular epithelial cells.
   C. NSAID induced AKI is often haemodynamically mediated but may be caused by acute interstitial nephritis.
   D. The diagnosis today of AKI rests on the serum creatinine which is imperfect marker of GFR.

MCQ Answers

1 = B; 2 = C; 3 = B

Extended Matching Questions

1. Acute kidney injury (AKI) is commonly iatrogenic.
   A. Renal artery stenosis/hypertension/chronic heart failure
   B. Pre-existing renal disease
   C. Small and large vessel arterial diseases
   D. Hypovolaemia

Match the disorders shown above with the therapy causing AKI. Each of the option can be used once, more than once or not at all.

1. Aminoglycosides
2. Radiologic contrast agents
3. NSAIDs
4. ACE inhibitors +diuretics

EMQ Answers

1. Aminoglycosides
2. Radiologic contrast agents
3. NSAIDs
4. ACE inhibitors +diuretics

A = 3, 4; B = 1, 2; C = 4; D = 1, 2

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Chronic Kidney Disease in the Elderly 33

Contents

Abstract

Chronic kidney disease (CKD) is characterized by a gradual and progressive loss of renal function resulting in permanent renal failure. The review provides an overview of chronic kidney disease, the clinical manifestations, complications and clinical management. CKD is a progressive disease. Hypertension, intraglomerular pressure, proteinuria and renal damage are interrelated in the background of CKD progression. Renal failure is assessed by the GFR as serum creatinine is a poor indicator of renal failure and one of the reasons being creatinine production is related to the muscle mass. In the elderly, nephrosclerosis, diabetes, obstructive uropathy, polycystic disease and glomerular disease cause renal failure. Chronic renal disease is a significant problem in the elderly and is associated with a high risk of renal failure and death. The aim of treatment is to control symptoms, reduce complications and slow the progression of the disease. Important diagnostic considerations are exclusion of potentially reversible causes such as urinary tract obstruction, the use of nephrotoxic agents and renal artery occlusion. Patients with CKD have a greater risk of dying of cardiovascular disease than progression to end-stage renal disease (ESRD), and there is a close relationship between heart failure and CKD.

Keywords

Chronic kidney disease · End-stage renal disease · Cockcroft–Gault formula · MDRD eGFR · Haemodialysis · Transplantation

Introduction

Chronic kidney disease (CKD) is characterized by a gradual and progressive loss of renal function resulting in permanent renal failure. It is defined as kidney damage or GFR <60 ml/min/1.73 m for 3 months or more irrespective of the cause

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_31

[1]. According to the US Renal Data System, there is a rising incidence and prevalence of renal failure and an increase of 104% in the prevalence of CRF between years 1990 and 2001 [2]. In an epidemiological study, the incidence of CKD was 260 patients per million population annually referred to nephrology units for CRF [3]. In the United States, the incidence of end-stage kidney disease in those over 75 years was four times that of the average population [4]. It increases at an unusual rate of 8% and utilizes up to 2% of the global health expenditure [5].

CKD is a progressive disease. Hypertension, intraglomerular pressure, proteinuria and renal damage are interrelated in the background of CKD progression. Hypertension is an important risk factor for disease progression [6–8]. Both the absolute blood pressure level and the physiological nocturnal decrease (dipping) may have a role in the progression of the disease [9]. It had been shown that the severity of the proteinuria correlates with the rate of renal failure progression [10], and reduction of the risk of CKD progression seems to be linked with proteinuria reduction [11, 12].

A five-stage classification of chronic kidney disease by the National Kidney Foundation [13] is as follows: stage 1, GFR normal or increased GFR, GFR >90 ml/mim; stage 2, mild renal damage decreased GFR, GFR 60–89 ml/min; stage 3, moderately decreased GFR, GFR 30–59; stage 4, severely decreased GFR, GFR 15–29 ml/min; and stage 5, kidney failure GFR <than 15 ml/min (or dialysis).

Renal failure is assessed by the GFR as serum creatinine is a poor indicator of renal failure, and one of the reasons being creatinine production is related to the muscle mass. The plasma concentration of urea and creatinine rises as the GFR declines in a non-linear fashion. There is normally a reduction in the GFR with ageing. The GFR at the age of 70 is about 2/3r that of the age of 30, and by the age of 80 or over, it is reduced to half the normal. The normal GFR is 120 ml/min. The GFR may be estimated by using the Cockcroft–Gault formula which calculates creatinine clearance based on serum creatinine, age, gender and body weight:

$$\text{Creatinine clearance}(\text{mL}/\text{min}) = \frac{[140 - \text{age}(\text{years}) \times \text{wt}(\text{kg})}{815 \times \text{Serum creatinine}(\text{nmol}/L)}$$

For females, it is multiplied by 0.85.

The normal range in males is 100–150 and females 85–130 ml/ml/1.73 m^2.

Although the Cockcroft–Gault formula is widely used, the Modification of Diet in Renal Disease (MDRD) equation is recommended. It is based on the effect of protein restriction and blood pressure control on the progression of the chronic renal disease. It is derived from the serum creatinine concentration, age, gender and adjusted to average adult body surface area (1.73 m^2). GFR(ml/mm/1.73 m^2) = 186(Pcr) − 1.504(age) × 0.203(0.742 if female) [14]. Both equations are derived from serum creatinine concentration which can be influenced by many factors, for instance, extremes of body size, dietary intake and diseases affecting the skeletal muscles.

The MDRD eGFR seems to predict GFR more accurately than the Cockcroft–Gault equation especially for values <60 ml/min/1.73 m^2. MDRD eGFR is used as a screening tool for chronic kidney disease. Chronic kidney disease may be present when the MDRD eGFR is <60, but because the MDRD is adjusted for average adult body surface, it does not provide an actual estimate of the patient's GFR. GFR declines with age, and for individuals aged 70 years and over, stable MDRD eGFR values from 45 to 59 ml/min in the absence of other signs of kidney disease may not be associated with complications of chronic kidney disease.

Causes of Chronic Kidney Disease

There are a variety of causes giving rise to chronic kidney disease. Diabetes, chronic kidney disease and cardiovascular disease show common risk factors and often occur together. In the elderly, nephrosclerosis, diabetes, obstructive uropathy, polycystic disease and glomerular disease cause renal failure. The most common cause of end-stage renal disease (ESKD) is diabetic nephropathy followed by hypertensive

nephrosclerosis and various primary and secondary glomerulopathies.

Clinical Manifestations and Complications

Chronic renal disease is a significant problem in the elderly and is associated with a high risk of renal failure and death [15]. The decreased renal function is associated with manifestations in virtually all organ systems. Irrespective of the primary cause, renal failure presents with common signs and symptoms. Fatigue, tiredness, anorexia, nausea and pruritus tend to dominate (Fig. 1).

High-output cardiac failure and fluid overload from anaemia may cause confusion with primary cardiac failure. Forty percent of patients with chronic kidney disease have cardiac failure and this further increased by 30% in those on dialysis [17]. Other cardiac manifestations include pericarditis which may progress to cardiac tamponade. Hypertension often complicates chronic kidney disease. Hypertension is an important factor in the progression of kidney dysfunction and the development of cardiovascular disease.

A bleeding tendency manifesting as mucosal bleeding, epistaxis, gastrointestinal bleeding and easy bruising occur with advanced renal failure. Anaemia of chronic renal failure is a normocytic normochromic anaemia and is due to a low or absent erythropoietin. Poor response to erythropoietin should suggest the need to exclude iron deficiency. Gastrointestinal bleeding often occurs and should be looked for. Erythropoiesis-stimulating drugs are effective in controlling the anaemia and hence enhancing the functional status.

Neurological problems contribute significantly to the morbidity and mortality in patients with chronic kidney disease. The neurological complications may be manifestations of central or peripheral nervous systems and may appear early or late in the course of the disease. They may be the result of the disease itself or the result of treatment, renal dialysis, renal transplantation or medications. Dialysis can directly or indirectly be associated with a number of complications such as dialysis dementia, disequilibrium syndrome, hypertensive encephalopathy, intracranial hypertension [18] and mononeuropathy, among others. Kidney transplantation or dialysis therapy may even induce neurological complications [19]. Cognitive impairment may develop in a considerable proportion of patients on dialysis and improves with renal transplantation [20]. Uraemic encephalopathy though less common with the advent of dialysis manifests as confusion, impaired cognitive function, asterixis, myoclonus and seizures. Peripheral sensory neuropathy could advance to motor neuropathy which is irreversible.

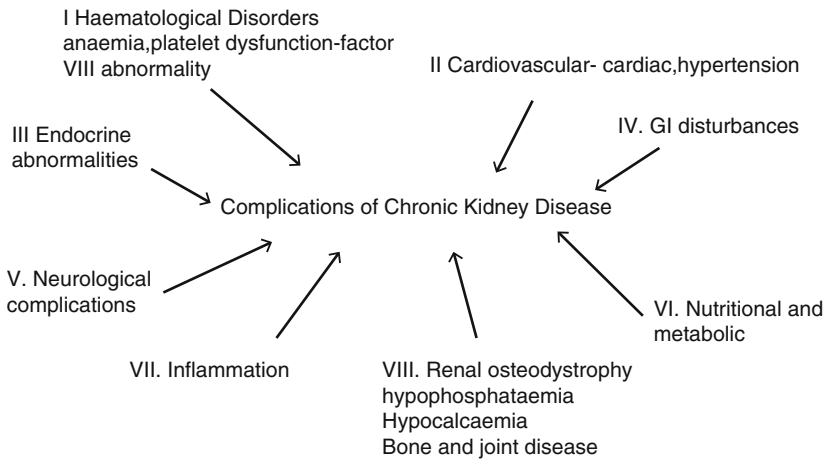

Fig. 1 Complications chronic kidney disease. http://www.nursingcenter.com/prodev/ce_article.asp?tid+=587028 [16]. Accessed on 12/9/08

Polyneuropathy occurs in 60% of patients with chronic renal failure – motor, sensory, autonomic and cranial nerves [21, 22]. Compression of the ulnar nerve in Guyon's canal at the wrist has occurred due to uraemic tumoural calcinosis [23]. Dietary modification and better dialysis in patients with peripheral neuropathy can improve outcomes of transplantation if implemented before surgery [18]. Progression of uraemic myopathy parallels the decline in renal function [24].

A broad spectrum of disturbances of bone metabolism occurs in CKD. These include, for example, effects of high levels of PTH resulting in osteitis fibrosa or mineralization defects resulting in osteomalacia [25]. In CKD, the term mineral and bone disorder had been recommended in place of 'renal bone disease' and 'renal osteodystrophy' [25]. Metabolic bone disease is a common complication of CKD both before and after dialysis. Progressive loss of renal nephrons leads to abnormalities in calcium and phosphate, vitamin D metabolism, parathyroid secretion and skeletal metabolism. Serious complications such as seizures, arrhythmias and respiratory problems can occur with imbalance of calcium, phosphorus and magnesium [26]. With functional loss of nephrons, there is frank hyperphosphatemia and hypocalcaemia as a result of a phosphate load presented to the remaining nephrons and as a consequence of a relative or absolute deficiency of calcitriol. Diminished vitamin D activity contributes to secondary hyperparathyroidism [27]. Renal osteodystrophy becomes evident due to major abnormalities of hyperparathyroid disease and defective mineralization. The bone changes result from a combination of different processes including secondary hyperparathyroidism, osteomalacia, osteosclerosis, osteoporosis and aluminium toxicity. Aluminium-containing agents have proven toxicity [28] and toxicity in uraemic patients result from the use of phosphate binders that include aluminium salts but decreased renal capacity to excrete aluminium. Secondary hyperparathyroidism manifests as subperiosteal resorption, intracortical tunnels and brown tumour; osteomalacia as coarsened fuzzy trabeculae, Looser's zones and osteopenia; osteoporosis as thinned cortices and osteopenia; osteosclerosis as 'rugger jersey spine'; and aluminium toxicity as Looser's zones and fracture of ribs.

A number of factors contribute to malnutrition in patients with chronic kidney disease. With progression of the disease, anorexia worsens, with diminution of the sense of taste. There is an overall reduction in the food consumed because of dietary restrictions – reduced protein, the use of phosphate binders and vitamin D supplementation for regulating hyperphosphatemia and hypocalcaemia. Patients with CKD are prone to infection and chronic inflammation which causes a decline in appetite, muscle and fat wasting and increased rate of protein depletion [29].

Treatment

The aim of treatment is to control symptoms, reduce complications and slow the progression of the disease. Once the diagnosis of CKD is established, the definite cause should be identified. Important diagnostic considerations are exclusion of potentially reversible causes such as urinary tract obstruction, the use of nephrotoxic agents and renal artery occlusion. Primary care physicians should be guided by the clinical practice guidelines in the Chronic Kidney Disease (CKD) Management in General Practice. It relates treatment recommendations in the earlier stages of kidney disease as well as indications for referral [30].

About one-third of the people with diabetes, which is the leading cause of CKD, may develop chronic kidney disease (CKD). ACE inhibitors/A II receptor blockers are used to reduce proteinuria and are very commonly used in diabetic renal disease. Vigorous glycaemic control will reduce the risk of development of CKD. Sulphonylureas should be avoided in stages 3–5 CKD [31]. The use of metformin in patients with diabetes and kidney disease has been a subject of debate. Lactic acidosis associated with metformin is estimated to occur in 1–5 per 100,000 [32]. Patients with hypoxaemic conditions such as myocardial infarction, severe infections, liver disease and respiratory disease are at risk of lactic acidosis [33]. It has been suggested that rather than avoiding the use of

metformin in patients with CKD, it can be used in CKD patients with GFR 60–90, with a reduced dose at lower levels of GFR, and it is probably safe and should be used with caution [33], more so in the elderly. The following guidelines have been formulated involving the use of metformin. Metformin should be ceased in patients with a serum creatinine level above 150 mmol/l; withdrawn during periods with suspected hypoxia, for instance, myocardial infarction or infection; withdrawn for 3 days after contrast medium containing iodine and restarted only after rechecking creatinine level; and withdrawn 2 days before general anaesthesia [34].

Hypertension should be controlled carefully. Lowering the blood pressure results in reduced cardiovascular risk in patients with chronic kidney disease. It is aimed that the blood pressure in patients with proteinuria more than 1 g/day be kept at 125/75 mmHg and in those with protein less than 1 g/day at <130/80 mmHg [35]. The first line of treatment in patients with chronic kidney disease and diabetes or proteinuria is the ACE inhibitors, and evidence suggest that renoprotection is achievable even in severe renal failure. ACE inhibitors, ARBs and beta blockers (carvedilol, bisoprolol and long-acting metoprolol) improve prognosis. Often it is noted that there may be a rise in the serum creatinine, and the drugs should be continued unless the rise is more than 30% above the baseline value. In such cases, patients should be investigated for renal artery stenosis. Their most common side effects include hypotension, hyperkalaemia and early decrease in GFR but usually could be managed without discontinuing the drug [36]. ACE inhibitors and ARBs should be withheld if potassium level is >6 mmol/l despite dose reduction. In elderly patients with non-proteinuric CKD, the use of ACEI and ARB may be harmful with an acute decrease in renal function, and in the elderly with renovascular disease, CKD may progress rapidly to ESKD. Several studies have shown the efficacy of combining ACEI or ARB monotherapy with other agents such as thiazide and non-dihydropyridine calcium channel blockers [37].

The use of NSAID should be avoided in elderly patients with CKD. NSAIDs can induce a reduction in prostaglandin synthesis and renal hypoperfusion resulting in AKI [38]. Vasoconstrictors angiotensin II and norepinephrine are increased in conditions with true volume depletion. Vasodilator prostaglandins act to preserve renal blood flow and GFR by relaxing preglomerular resistance. In such patients, NSAIDs by inhibiting prostaglandin synthesis can lead to AKI. NSAIDs also cause AKI due to acute interstitial nephritis [39]. The risk of AKI increases severalfolds with NSAID when used together with a loop diuretic and may become extremely hazardous if ACEI and ARB are included. The dose of allopurinol requires adjustment in elderly patients with renal dysfunction. eGFR is a good guide in determining the starting dose of allopurinol.

Iron deficiency is treated with oral iron. Intravenous infusion of iron polymaltose (500 mg) or iron sucrose is used when there are adverse effects to oral iron. Ferumoxytol, a new intravenous IV iron product, was found to be substantially safe and efficient compared to oral iron therapy and can be administered in less than 1 min [40]. It has the advantage of not requiring a test dose and can be administered in the outpatient setting [41]. It is generally well tolerated in both non-dialysis- and dialysis-dependent patients and more effective than oral iron [42]. Dizziness, nausea, pruritus and headache had been reported in less than 2% of the patients who had received ferumoxytol [43]. Erythropoietin or iron may be needed to control the anaemia and is indicated when the haemoglobin is below 10 g/dl. Epoetin alfa (erythropoietin EPD) is generally started at a dose of 50–100 u/Kg three times per week IV in dialysis patients and subcutaneous in others. There are several supplementary epoetins other than epoetin alfa, namely, epoetin beta, which is said to be less painful, and darbepoetin alfa which has prolonged action. There was no significant difference between epoetin alfa and epoetin beta in terms of Hct level [44]. During the maintenance phase, the primary care physician can undertake the monitoring of the haemoglobin level once in 2–3 weeks and iron studies every 3 months. The mortality and morbidity such as increased risk of

thrombotic events are said to increase with higher haemoglobin targets, and it is recommended that the haemoglobin target should be 11–12 g/dL for all patients [45]. Randomized trials have shown an increase in the frequency of cardiovascular events in patients whose haemoglobin levels are maintained above 13 g/dl with erythropoietin (ESA) therapy [46]. The Kidney Disease Improving Global Outcomes (KDIGO) publication of guidelines in 2012 for anaemia in CKD had recommended that the injectable iron rather than oral should be the first line of treatment for anaemia associated with CKD. ESA is used when the haemoglobin is less than 100 g/l, and cautious use of blood transfusion is needed if there is transplantation potential [47].

Attempts to prevent renal osteodystrophy ideally starts early in the course of CKD. In early GKD, dietary restriction of phosphorus may be used to control the developing hyperparathyroidism [25]. Treatment includes the use of dietary phosphate restrictions, the use of phosphate binders (e.g. calcium carbonate, magnesium trisilicate), vitamin D supplementation with calcitriol or vitamin analogue such as paricalcitol. There are limitations to the use of calcium-based phosphate binders which may lead to increase in calcium loads and vascular calcifications in patients with ERSD and on haemodialysis [25] Alternately, non-calcium-containing phosphate binders such as sevelamer hydrochloride or lanthanum carbonate [28] have been shown to promote phosphate control while limiting calcium intake [48]. Lanthanum carbonate appears to be effective as monotherapy, but the efficacy of sevelamer in lowering phosphate levels in severe hyperphosphatemia is questionable [28]. Active vitamin D sterols and vitamin D analogs are useful to control hyperparathyroidism in patients with advanced kidney disease [25].

Calcimimetic agents such as cinacalcet (Sensipar) are used to control hyperparathyroidism in patients with ESKD and are effective in reducing PTH levels [24] and its use is evolving. It is said to enhance the sensitivity of calcium receptors to calcium in the parathyroid glands and suppress PTH secretion. Treatment is aimed at keeping the serum calcium level in the normal range, the phosphate below 1.65 mmol/l and PTH two to three times the upper reference limit [49].

If hypocalcaemia persists after normalization of phosphate, it should be treated with vitamin D (calcitriol). Because vitamin D increases phosphate absorption, dosage levels of phosphate binders may have to be adjusted. Phosphorus intake should be limited to 800–1,000 mg/day. Dairy products have a high content of phosphates and a good starting point is to limit or eliminate dairy products.

Fluids should be restricted to an amount equal to the volume of urine passed. Fluid sufficient to produce 2–3 L of urine/day when the fluid intake equals the amount of urine passed plus 500–800 ml/daily. Protein and salt restriction are often needed to suppress volume expansion and blood urea nitrogen (BUN) elevations. Pruritus is a problem in the elderly uraemic patients especially those with xerosis. Ultraviolet treatments and skin moistures are found to be effective.

Infections are the second commonest cause of death in ESKD [50]. It also contributes to increased morbidity in patients in the earlier stages of CKD [51]. Patients with CKD are immunocompromised due to impaired cell mediated and humoral immunity and decreased activity of the immune system. This results in their having a lower seroconversion rate, low peak of antibody titres and a greater decline in antibody levels as compared to the healthy [52]. There is an emerging evidence of benefits to vaccination in patients with CKD. Although CKD and ESKD patients may not respond as well to many vaccines as patients without kidney disease, some vaccines such influenza retain their efficacy and reduced infection rates with standard immunization schedules [50]. Others like pneumococcal vaccine and hepatitis B vaccine may require frequent boosters and higher doses [50]. It is essential that immunization should be adapted and not avoided [53].

Impact

CKD is common in the elderly [54, 55] and the number of person's with CKD in the United States is expected to double within 10 years [56]. Increased health-care costs and mortality are associated with older people with CKD. CKD increases the risk of not only cardiovascular diseases but all causes of mortality and these result in increased costs [57]. Patients with CKD have a greater risk of dying of cardiovascular disease than progression to end-stage renal disease (ESRD), and there is a close relationship between heart failure and CKD [58]. About 40% of heart failure patients have CKD [58]. Persons older than 70 years with CKD have double the risk for physical impairment, frailty and cognitive dysfunction [59]. Patients with advanced CKD have severe psychological disorder, and about 25% of patients on haemodialysis have clinical depression and are associated with low quality of life and increased mortality [60]. Depressive symptoms and pain are common in patients with CKD on chronic haemodialysis, and the former and to a lesser extent the latter are independently associated with reduced HR-QOL [61]. In patients with CKD, QOL is affected by such factors as age, anaemia, co-morbidities and depression, and many of these factors are present prior to dialysis, and it has been shown that replacement therapy improves the QOL [62]. In elderly patients on dialysis with CKD, chronic pain is a common occurrence, and pain management and improving physical and mental symptoms will have an impact on the well-being of the patient [56]. Instrumental activities of daily living (IADL) and activities of daily living (ASL) decline in community-dwelling older patients with CKD [63]. Heightened inflammatory state is the likely mechanism resulting in the development of functional impairment in patients with chronic kidney disease, and this is independent of body composition, co-morbidity and physical performance [64]. Treating the elderly patient with dialysis is challenging due to the increased costs, multiple co-morbidities, the perceived minimal long-term benefit and increased mortality [65]. The American Society of Nephrology and the Renal Physicians Association laid down guidelines on the initiation, withholding and withdrawal of dialysis emphasized on a shared decision including the patient, the family and the treating physician [66] (Box 1).

Box 1 Key Points: Chronic Kidney Disease (CKD)

It is defined as kidney damage or GFR <60 ml/min/1.73 m(2) for 3 months or more irrespective of the cause.

Progressive renal failure eventually leads to uraemic syndrome and end-stage renal disease (ESKD).

Renal failure is assessed by the GFR as serum creatinine is a poor indicator of renal failure.

The GFR may be estimated by using the Cockcroft–Gault formula which calculates creatinine clearance based on serum creatinine, age, gender and body weight.

eGFR is a useful marker of CKD.

For patients with eGFR 15–30 ml/mm/1.73m^2 and those with eGFR <15 ml, referral to a nephrologist is usually required for consultation and continued monitoring.

In patients with moderately reduced eGFR (30–60), the blood pressure, blood sugar, cholesterol, smoking and obesity should be treated. If appropriate, ACEs and ARBs should be used and nephrotoxic drugs avoided.

Anaemia, acidosis and hyperparathyroidism should be attended to.

Early diagnosis and treatment often can prevent or delay some adverse outcomes of GKD.

For patients with diabetes and end-stage ESKD, immunization against influenza and invasive pneumococcal disease is

(*continued*)

Box 1 Key Points: Chronic Kidney Disease (CKD) (continued)
recommended by NHMRC. Pneumococcal vaccine and hepatitis B vaccine may require frequent boosters and higher doses [50]. It is essential that immunization should be adapted and not avoided [53].

Multiple Choice Questions

1. The following are true of chronic kidney disease (CKD), except:
   A. CKD is common in the elderly and is associated with substantial mortality and morbidity.
   B. The incidence of CKD is falling rapidly.
   C. Diabetes and hypertension are important factors in the progression of kidney dysfunction.
   D. CKD patients are at higher risk of cardiovascular death than progression to end-stage renal disease (ESRD).
2. The following are true of chronic kidney disease (CKD), except:
   A. The glomerular filtration rate (GFR) at age 70 is about two-thirds of the age of 30 and by the age of 80, it is half normal.
   B. CKD is defined as a GFR <30 ml/min/1.73 m^2.
   C. The plasma concentration of urea and creatinine rises as the GFR declines in a non-linear fashion.
   D. eGFR is a useful marker of CKD.
3. In a patient with chronic kidney disease (CKD), the following are true, except:
   A. Anaemia of CKD is normocytic normochromic and is due to low or absent erythropoietin.
   B. Poor response to erythropoietin should suggest the need to exclude iron deficiency.
   C. Lowering the blood pressure results in increased cardiovascular risk in patients with CKD.
   D. Neurological complications may be the result of treatments – renal dialysis, renal transplantation or medication.
4. The following are true of chronic kidney disease (CKD), except:
   A. With functional loss of nephrons, there is frank hyperphosphataemia and hypocalcaemias.
   B. Bleeding time is shortened in CKD.
   C. Diminished vitamin D activity contributes to secondary hyperparathyroidism.
   D. A high parathyroid hormone (PTH) level characterizes a high turnover renal bone disease.
5. The following are true of chronic kidney disease, except:
   A. Erythropoietin or iron may be needed to control anaemia when haemoglobin is below 10 g/dl.
   B. The haemoglobin target should be 11–12 g/dl for all patients; higher haemoglobin levels increase mortality and morbidity.
   C. Dairy products need not be limited or eliminated from the diet for CKD patients.
   D. If hypocalcaemia persists after normalization of phosphate, it should be treated with vitamin D (calcitriol).

MCQ Answers

1 = B; 2 = B; 3 = C; 4 = B; 5 = C

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Prostate Gland and Related Disorders 34

Contents

Abstract

The transition zone of the prostate enlarges with age by developing benign prostatic hypertrophy, and the proliferative process occurs exclusively in the transition zone and periurethral glands. Benign prostate hypertrophy (BPH) is a common part of ageing, and by the age of 80 years, about 90% of the men will have histological evidence of BPH. The diagnosis is based on the history followed by digital rectal examination (DRE) which is an integral part in the evaluation. Prostatitis is an inflammatory disorder, bacterial or nonbacterial and can be acute or chronic. Prostatic abscess is a focal accumulation of pus within the prostate. Carcinoma of the prostate is the commonest malignancy among elderly men affecting 30% of men at the age of 50 and 90% at the age of 90 years. The review summarises the main group of prostate disorders with the main focus on the management.

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_34

Keywords
Benign prostatic hypertrophy · Prostatitis · Prostatic abscess · Carcinoma of the prostate

Introduction

The adult prostate gland is made up of glandular (70%) and nonglandular tissue (30%) [1], and the former is divided into three zones [1, 2]. The central zone comprises about 25% of the gland, the peripheral zone about 70% and the transition zone about 5% [1]. Within the periprostatic fat in the posterolateral part of the peripheral zone are the neurovascular bundles which give off branches into the apex and base of the prostate [3]. It secretes an alkaline fluid that comprises a large portion of the seminal fluid [1].

Benign Prostate Hypertrophy (BPH)

The central zone is the greatest in the young and atrophies with advancing age. The transition zone enlarges with age by developing benign prostatic hypertrophy, and the proliferative process occurs exclusively in the transition zone and periurethral glands [4, 5]. BPH is a common part of ageing, and by the age of 80 years, about 90% of the men will have histological evidence of BPH [6]. It has been postulated that testosterone plays a role in its development. As man ages, the amount of the testosterone produced decreases with proportionate increase in the oestrogen levels within the gland, and this increases the activity of the substances that promote cell growth [7]. Testosterone is converted to dihydrotestosterone (DHT) by enzyme 5-alpha reductase (5AR), and there are two types of 5-alpha reductase, and type 2 is the primary subtype in the prostate [8]. The androgen 5-alpha dihydrotestosterone (DHT) binds to the androgen receptors and can result in BPH [7]. DHT promotes development and growth of the prostate, but there is no direct correlation between DHT and possible growth [8]. BPH involves both the stromal and epithelial elements of the prostate arising in the periurethral and transition zones and is normally dependent on testosterone and DHT production. Males who are deficient in 5AR will not be able to convert intraprostate testosterone into DHT [9] and will not develop BPH [10].

Static and dynamic factors contribute to the bladder neck obstruction in BPH [11]; the former is due to prostatic enlargement and the latter to the tension in the prostate smooth muscle [4]. In the pathophysiology of clinical BPH, the prostate and/or prostatic urethra plays an important role [4]. In vitro studies have shown that, in the capsule of the prostate, the smooth muscle of the stroma and the bladder neck, there are localised large amounts of alpha-1 adrenergic receptors. Stimulation of these receptors gives rise to increase in the smooth muscle tone which can worsen lower urinary tract symptoms (LUTS) [7]. Some of the LUT symptoms are attributable to the ageing of the bladder, and age-matched men and women have similar levels of LUTS [12]. The obstructive-induced bladder contributes significantly to the symptoms. The bladder wall becomes thickened, trabeculated and irritable. It hypertrophies to increase its contractile force. Even with small volumes of urine in the bladder is believed to cause urinary frequency and LUTS because of the detrusor instability. The bladder gradually weakens and loses its ability to empty completely thus leading to increased residual urine volume.

Symptomatology

One of the early symptoms is the need to get up at night to urinate. Other symptoms include an urge to urinate frequently during the day, hesitancy, urgency, interrupted weak stream, leaking or dribbling. These symptoms can also be produced by other disorders, namely, prostatic infection, urethral stricture, prostate cancer and medications.

Diagnosis

The diagnosis is based on the history followed by digital rectal examination (DRE) which is

an integral part in the evaluation. During DRE, the finger pads are swept across the rectal surface and the prostate palpated. It is useful for the general practitioner to estimate the gland size, contour, tenderness and presence of nodules and evaluate areas suggestive of malignancy and the presence or absence of fluctuance and pain in prostatic abscess. Transrectal ultrasonography (TRUS) can be used for a more precise volumetric determination. Other investigations include, PSA, urine analysis, urine for culture, electrolytes, urea and creatinine. Imaging using TRUS is indicated for patients with elevated PSA levels, and a TRUS-guided biopsy may be indicated. Urinary flow study, intravenous pyelogram and cystoscopy are optional.

Most doctors consider PSA level below 4 ng/ml as normal [13]. A high PSA level does not mean that it is cancer, and a low level does not mean it is definitely not [14, 15]. PSA levels can rise with prostatitis or urinary tract infection, and it can be low with finasteride and dutasteride [13]. If biopsy is done, approximately twice as many men with PSA levels above 4.0 will have prostate cancer in the range of 40–50% [16]. That two men with identical PSA level can have different risks of prostate cancer will depend on other risk factors [15].

Other factors which increase the risk of developing prostate cancer are:

(i) Age (64% of cancer of the prostate in men 65years and over) [17]
(ii) Family history [17].
(iii) Ethnicity [17]
(iv) Diet rich in fats [18]

DRE is most helpful when coupled with PSA. The PSA level of 3.0 ng/ml taken together with the DRE findings is very suggestive of benign hypertrophy of the prostate.

The American Urological Association (AUA) symptom index is the most widely accepted tool for quantifying the severity of the symptoms [19] (Box 1).

Box 1 American Urological Association Prostate Symptom Score

Over the past month
i. How often have you had the sensation of not emptying your bladder completely?
ii. How often have you had to urinate again in less than 2 h?
iii. How often have you stopped and started when urinating?
iv. How often have you found it difficult to postpone urinating?
v. How often have you had a weak urinary stream?
vi. How often have you had to push or strain to begin urinating?
Not at all = 0; less than 1 time in 5 = 1; less than half the time = 2; about half the time = 3; more than half the time = 4; almost always = 5
vii. How many times did you typically get up to urinate from time you went to bed until you got up in the morning?
None = 0, once = 1, twice = 2, thrice = 3, four times = 4, five times or more = 5
Mild BPH = 1–7; moderate = 8–10; severe = 20–35

Management

Watchful Waiting

At the individual level, the natural history of BPH is said to be highly variable [3]. Individuals with a low American Urological Association (AUA) [20] prostate symptom score (0–7) and those with moderate to severe symptoms and AUA score >8 but who are not inconvenienced and with no signs of complications of BHP should be watched (Box 2).

Box 2 Treatment of BHP

Watchful waiting
Medical
Alpha-blockers
5-Alpha reductase blocker
Surgical
TURP (transurethral resection of the prostate)
TUIP (transurethral incision of the prostate)
Open prostatectomy
TUMT (transurethral microwave thermotherapy)

Table 1 Medications used in the treatment of BPH

Type	Drugs	Side effects	Response
I. Alpha-blockers (selective agents)		Dizziness, fatigue	Effective against a wide range of prostate sizes
		Ejaculation disorders	
i. Selective short-acting alpha-1 blocker	Prazosin, alfuzosin	Nasal congestion	
	Indoramin	Postural hypotension	
ii. Selective long-acting alpha-1 blocker	Terazosin, doxazosin		
iii. Partially subtype alpha-1a-selective agent	Tamsulosin		
II. 5-alpha reductase inhibitors	Finasteride Dutasteride	Decrease in libido Erectile dysfunction Ejaculation disorder	Reduces level of DHT by 80% may take several months before activity is noted

Medical Management

Over the last few decades, the medical therapeutic options have increased and have given rise to receptor specific alpha-blockers. Basically they can be categorised into two groups (Table 1):

i. The alpha-blockers that inhibit contraction of the prostatic smooth muscle, urethra and bladder neck
ii. The 5-alpha reductase inhibitors that lower the prostatic androgen levels

Prostatic enlargement depends on androgen 5-alpha DHT. Circulating testosterone is metabolised by the type ii 5-alpha reductase into DHT which binds to androgen receptors in the cell nuclei, and this can result in BPH [7]. 5-Alpha reductase inhibitors block the activity and thereby inhibit DHT-receptor complex formation. Individuals with moderate enlargement of the prostate are at risk of acute retention of urine and according to Lepor [8] high enough to warrant the use of 5-alpha reductase inhibitors. It has been shown that long-term use of 5-alpha reductase inhibitors finasteride and dutasteride causes reduction of prostate volume and also prevents further growth [8, 21, 22].

Surgical Management

Surgery is the most effective treatment for BPH. It is also the first choice for those individuals with high AUA symptom score. However the use of surgery for BPH has declined substantially with the advent of improved drug therapy [18]. Open prostatectomy and TURP are the most effective in producing increased urine flow rate. In o*pen prostatectomy*, the prostate is removed by lower abdominal incision. The inner portion of the prostate is removed by endoscopic approach in *transurethral resection of the prostate (TURP)* and has been acknowledged as the standard for relieving bladder outlet obstruction secondary to BPH [7]. *Transurethral incision of the prostate (TUIP)* is an endoscopic procedure whereby one or two cuts are made in the prostate to reduce the constriction of the urethra. In *balloon dilatation*, a balloon is inserted through the urethra and inflated to stretch the narrowed urethra. In *transurethral microwave thermotherapy (TUMT)*, a microwave tube placed in the urethra causes deep rapid heating around the urethral base (Boxes 3 and 4; Table 2).

Box 3 Indications for TURP
Failed voiding trials;
Acute urinary retention;

(*continued*)

Box 3 Indications for TURP (continued)
Gross haematuria;
Urinary tract infection;
Secondary to obstruction;
Failure of medical therapy;
A desire to terminate medical therapy.

Box 4 Key Points: Benign Prostate Hypertrophy
One of the early symptoms is the need to get up at night to urinate.

Other symptoms include an urge to urinate frequently during the day, hesitancy, urgency, interrupted weak stream, leaking or dribbling.

The diagnosis is based on the history followed by digital rectal examination (DRE) which is an integral part in the evaluation.

Over the last few decades, the medical therapeutic options have increased [17] and have given rise to receptor specific alpha-blockers.

Box 4 Key Points: Benign Prostate Hypertrophy (continued)

Transurethral resection of the prostate (TURP) has been acknowledged as the standard for relieving bladder outlet obstruction secondary to BOH [7].

Acute and Chronic Prostatitis

Introduction

Prostatitis is an inflammatory disorder, bacterial or nonbacterial and can be acute or chronic. Reported rates of prostatitis are similar in North America, Europe and Asia [23], and its estimated prevalence is about 9% in the community [24]. About 90–95% of the cases are due to chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [25, 26]. The National Institute of Health has classified prostatitis into four categories, namely, acute bacterial, chronic bacterial, chronic nonbacterial, and pelvic pain syndrome and asymptomatic inflammatory prostatitis [23, 27].

Table 2 Surgical management of BHP

Surgical procedure	Indication	Morbidity	Result	Comments
i. Open prostatectomy	Large bulky prostate, structural median prostate lobe	High	Most effective	Hardly done now
ii. Transurethral resection as in box of prostate (TURP)		Complications: early blood clot retention, secondary infection, inability to urinate, late-retrograde ejaculation impotence and urinary incontinence	Relieves symptom in 90% 0f cases	Common surgical procedure; elderly numerous medical problems – poor condition; requires repeat within 5 years
iii. Transurethral incision		Smaller of prostate (TUIP)	Less bleeding	As for TURP prostates
iv. Transurethral microwave thermotherapy (TUMT)		No major complications	70% decrease in symptoms	10% require repeat after 2 years
v. Balloon dilatation				

Information sources: Levelliee et al. [7]

Symptomatology

Acute bacterial prostatitis usually presents with systemic symptoms such as high fever, chills, malaise, urinary urgency, frequency, perineal pain and symptoms of obstructed voiding. In chronic prostatitis, the patient may be asymptomatic or with symptoms associated with back pain, frequency, dysuria and perineal pain. In CP/CPPS, the symptoms are similar to acute or chronic prostatitis and include perineal or low back pain, lower urinary symptoms and painful ejaculations [28], and the existence of pelvic pain is requisite for the diagnosis [29].

Treatment

In severe acute prostatitis, hospitalisation and intravenous broad-spectrum antibiotics (an aminoglycoside and beta-lactam combination or fluoroquinolone) [28] are needed until patient is afebrile followed by oral therapy usually for 4 weeks [30]. Chronic bacterial prostatitis is treated with fluoroquinolone involving a 4–8 week course [28, 30]. There are no specific guidelines for the treatment of CP/CCPS [8]. A single course of antimicrobial for 4–6 weeks may be beneficial [28]. In addition, a wide variety of therapies including alpha-blockers [28], anti-inflammatory medications and other agents such as finasteride and gabapentinoids have been used [31].

Prostatic Abscess

Introduction

Prostatic abscess is a focal accumulation of pus within the prostate [32]. Prostatic abscesses are rare [33, 34] and are often underdiagnosed [35], or there is a delay in diagnosis [33]. The incidence has decreased with the use of early antibiotics [35].The prevalence is about 0.5% of all prostatic disorders [36]. It is reported most commonly in the age group between 50 and 60 years [33]. There has been a shift in the mortality rate from 6% to 30% in the 1940s to 3–16% recently [34, 37]. It may be a complication of acute prostatitis [38] or a retrograde flow of contaminated urine [39].

Symptomatology

Patients present with dysuria, frequency, perineal pain or urinary retention, and some of them may have systemic symptoms such as fever and chills [33].

Diagnosis

It is often difficult to diagnose [34, 35], and the differential diagnosis is with acute prostatitis [35].The abscess could rupture into the rectum or perineum. Rectal examination may reveal tenderness and an enlarged and fluctuant prostate. The finding of tender fluctuant prostate on rectal examination is not a common occurrence [35]. In some blood cultures will be positive. The urine may be normal or there may be pyuria or bacteriuria.

Treatment

Small abscesses less than 1 cm are treated with antibiotics such as fluoroquinolones for a minimum of 4–6 weeks [40]. Larger abscesses require surgical drainage [40], and percutaneous transperineal or transrectal drainage under transrectal sonography or CT-guided drainage [40] is the first choice for therapy [32]. Once an abscess is diagnosed, antibiotic therapy should be commenced and drainage performed [32] (Box 5).

Box 5 Key Points: Prostatitis

The National Institute of Health has classified prostatitis into four categories, namely, acute bacterial, chronic bacterial, chronic nonbacterial, pelvic pain syndrome and asymptomatic inflammatory prostatitis.

Carcinoma of the Prostate

Introduction

Carcinoma of the prostate is the commonest malignancy among elderly men [41, 42] affecting 30% of men at the age of 50 and 90% at the age of 90 years [5]. It is the second leading cause of cancer in the Western world [41] with increasing incidence with age [43]. The incidence of prostate cancer increases sharply after the age of 55 and peaks at age of 70–74 and slightly decline thereafter [17]. Men over the age of 65 years account for 68% of disease and 92% mortality [44]. There is a very high death rate from prostate cancer in the Scandinavian countries [45], and in Japan, it is relatively low [45] with the United States adopting an intermediate position. It is known that immigrants from countries with low incidence acquire an intermediate risk when they migrate to countries of high risk [45]. The aetiology is not known, but it increases with age. It has been suggested that hormonal changes of old age may be associated with its causation.

Adenocarcinoma begins in the peripheral zone in 70% of cases but can arise elsewhere, and 29% originate in the transition zone and 19% in the central zone [46]. Prostatic intraepithelial neoplasia (PIN) is widely deemed to be the likely forerunner of invasive prostatic cancer [47]. PIN is characterised by cellular proliferation within pre-existing ducts and glands with cytological changes [48]. Not all high-grade PIN develop into invasive disease, but high-grade PIN, age and PSA are decidedly indicative of prostatic cancer [49].

Clinical Expression

The patient may be asymptomatic or may present with symptoms and signs of prostatism, rarely with haematuria or acute retention. Other symptoms are due to bone metastasis, bone pain or pathological fracture.

Diagnosis

The diagnosis of prostate cancer is made by using a range of tests:

i. Prostate-specific antigen (PSA) test. The prostate secretes a protein called PSA, and only little of it leaks into the blood stream. The PSA level rises with age as does the prostate size. In cancer of the prostate, large amounts of PSA enter the blood. The interpretation of PSA levels is not necessarily straightforward. The PSA can detect cancer in the early stages, but the PSA is not always conclusive of cancer, and no PSA level rules cancer in or out [15]. It can be raised in other conditions such as in benign hypertrophy of the prostate, prostatitis, after vigorous prostate massage, instrumentation such as cystoscopy and insertion of urinary catheters and vigorous physical activity such as cycling. The 'normal' value of the total PSA is age dependent, but the higher the total PSA levels are, the more likely it is to be cancer.

In normal individuals and in those with prostate cancer, the PSA is bound to protein. One form of PSA, free PSA, is not bound. Free PSA is sometimes requested when the total PSA is mildly elevated. The detection of free PSA and estimation of the free and total PSA (F/T) have been widely used for improving diagnostic accuracy and especially for increasing specificity [50, 51] and are useful in distinguishing between benign and malignant disease when the total PSA levels are in the grey area range between 2 and 10 ng/ml and useful when values are between 2.5 and 4.0 ng/ml. A free PSA that is less than 25% or less of the total PSA is indicative of increased risk of prostate cancer. A free PSA above the 25% threshold might suggest avoiding immediate biopsy. More recently the proenzyme of PSA, pro-PSA, was found to be a better marker of prostate cancer when the total PSA is between 2 and 10 ng/ml.

Screening with PSA for prostate cancer remains debatable [52]. There is evidence of widespread and increasing PSA testing in Australia largely [53]. The large scale of PSA screening

programmes may contribute to overdiagnosis of prostate cancer [54]. Prostate cancer-specific mortality has not decreased significantly with prostate cancer screening [55]. Although PSA testing has the potential to benefit some men by diagnosing potentially curable early-stage disease, it may be harmful to others with slow-growing cancers that are clinically insignificant and do not require invasive treatment [53]. Screening did not significantly reduce prostate cancer-specific mortality as revealed in a meta-analysis of the five RCTs [53]. The study also revealed that overdiagnosis and overtreatment were common and were associated with treatment-related harms [55].

It is imperative that men requesting PSA test are appropriately informed [31] about the risk of cancer, the possible benefits, limitations and implications of PSA testing prior to being tested. To overcome the possible harms of PSA screening, other approaches to allay them would be to include a higher PSA threshold for biopsy, considering biennial screening and a conservative therapy for men receiving a new diagnosis of prostate cancer [51]. PSA levels and risk of cancer: <4 ng/ml – normal; 4–10 ng/ml, 20–30%; 10–22 ng/ml, 50–75%; above, 20–90%.

DRE forms an integral part in the diagnosis to feel the size and any other abnormalities, and if one or the other is abnormal, a biopsy is done, guided by ultrasound known as the transrectal ultrasound (TRUS). Further tests are done if the results are positive to determine the stage of progression of the disease: bone scan and computerised tomography.

Gleason's Grading and Score

Although the Gleason grading and score are largely subjective, it had remained the most widespread method of prostate cancer tissue grading. Gleason grades range from 1 (well differentiated) to 5 (undifferentiated) with 5 having the worse prognosis. Gleason score ranges from 2 to 10 with 10 having the worse prognosis. The pathologists identify two architectural patterns and assign grades to each one. Grades 1 and 2 are well differentiated, the glands are well formed, and the cells appear pale; grade 1 is more compact. Grade 3 shows infiltration of cells from glands into the stroma and the cells are dark. In Grade 4, there is loss of architecture with irregular mass of cells and few glands. Grade 5 shows no attempt at gland formation; sheet of cells is seen throughout Gleason score. The pathologist identifies two architectural patterns and assigns a Gleason grade to each one: (i) the predominant pattern and (ii) the next most predominant pattern. The lowest possible Gleason score is 2 (1 + 1) where the first and the second patterns have a Gleason grade of 1. The highest Gleason score is 10 (5 + 5). The Gleason grading system remains a robust prognostic factor for prostate cancer largely because it allows gradual alterations by urological pathologists to comply with the changing practice of medicine [55].

In 2005 the International Society of Urological Pathology modified the Gleason system [56, 57]. Gleason 2–4 should hardly ever be diagnosed on needle biopsy [56]. What was graded 2–4 on the original system is now considered as Gleason score 6 in the modified system, and what was 6 earlier is now Gleason score 7 tumours [58]. It is believed that the effect of the 2005 modification has been to improve the perceived cancer-specific survival by 2 % through the Will Rogers phenomenon [59]. Carter et al. [58] felt that the modified Gleason grading system is misleading to both physician and patient. They argued the pros and cons for removing the label of cancer from Gleason 6 tumours and proposed an alternative modification. The findings of the study by Billes et al. [60] indicated that the recommendation of the 2005 modification is an estimable refinement of the standard Gleason grading system.

Treatment

The treatment of cancer of the prostate would depend on the grade of the cancer, the stage of the cancer, the age of the patient, life expectancy, patient's health condition and patient's preferences (Box 6). New treatment options include laparoscopic radical prostatectomy, robot-assisted laparoscopic radical prostatectomy and third-generation cryotherapy which are reassuring [61]. Curative therapy (radical prostatectomy, external beam radiotherapy and brachytherapy) normally is recommended for patents predicted to have a life expectancy of 10 years

[62]. With the advent of a variety of new agents, the therapeutic options in castrate-resistant prostate cancer have changed [63].

Impact

With increasing age, majority of prostate cancer patients develop microscopic disease, but only a few will endure invasive prostate cancer [54]. In the elderly, the impact of localised prostate cancer will depend on disease aggressiveness and life expectancy [63]. The choice of treatment options will be influenced by life expectancy, health status, lifestyle and available treatment. In the elderly, there are several diseases virtually involving all organ systems resulting in increased morbidity [64] and if not corrected may lead to death. In oncology practice, comorbidity is an important concern especially in older patients [65]. Hence an overall evaluation of the comorbidities ensures a comprehensive assessment of physical illness burden which can be used as a variable in predicting outcome [66]. Comorbidity and age have been shown to affect for treatment decisions and survival outcomes in prostate cancer [62]. Erectile dysfunction after radical prostatectomy has a profound effect on the quality of life (QoL); 76% who were potent before radical prostatectomy were impotent afterwards [67].

Box 6 Key Points: Cancer of the Prostate

- The patient may be asymptomatic or may present with symptoms and signs of prostatism, rarely with haematuria or acute retention.
- Other symptoms are due to bone metastasis, bone pain or pathological fracture.
- The diagnosis of prostate cancer is made by using a range of tests: (i) Prostate-specific antigen (PSA) test; (ii) DRE, which forms an integral part in the diagnosis to feel the size and any other abnormalities; and (iii) if biopsy, done if one or the other is abnormal, guided by ultrasound known as the transrectal ultrasound (TRUS).
- PSA and DRE should be offered to all men 50 years or older and in those with a family history of prostate cancer.
- Treatment of cancer of the prostate would depend on the grade of the cancer, the stage of the cancer, the age of the patient, life expectancy, patient's health condition and patient's preferences.

Multiple Choice Questions

1. The following are true of benign prostate hypertrophy, except:
   A. Prostatic-specific antigen (PSA) is normal.
   B. Most commonly affects the median lobe of the prostate gland.
   C. The diagnosis is based on the history followed by digital rectal examination (DRE).
   D. 5-Alpha reductase inhibitors finasteride and dutasteride cause reduction of prostate volume and also prevent further growth.
2. The following are true of cancer of the prostate, except:
   A. The bone lesions are osteolytic rather than osteosclerotic.
   B. Eighty percent of prostate cancer have a nonaggressive form.
   C. Histologically most lesions are adenocarcinoma with varying degrees of differentiation.
   D. The patient may be asymptomatic.
3. The following in benign hypertrophy of the prostate are true, except:
   A. BPH is associated with enlargement of the lateral lobes.
   B. It is rare under the age of 60 years.
   C. The anatomical zone involved in hyperplastic growth that occurs in BPH is the transitional zone.
   D. One of the early symptoms is the need to get up at night to urinate.

MCQ Answers

1 = A; 2 = A; 3 = A

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Male Sexual Dysfunction: Erectile Dysfunction (ED)

35

Contents

Abstract

There is a worldwide increase in erectile dysfunction. The prevalence of ED increases with age. It increases by 10% per year of age; it increased from 2% in age group 18–38 years to 48% in the over 70 years and older. Organic causes account for a large proportion of erectile dysfunction in the elderly than in the young. The clinician should appreciate the sensitivity of the situation and must avoid creating any unnecessary embarrassment and anxiety. Male erectile dysfunction has a significant impact on health-related quality of life. The review discusses the prevalence and the causes followed by evaluation and clinical management.

Keywords

Erectile dysfunction · Organic causes · Phosphodiesterase (PDE5) inhibitors

Introduction

Erectile dysfunction (ED) is characterised by an inability to attain and sustain an erection sufficient for satisfactory sexual intercourse. There is a worldwide increase in erectile dysfunction. The prevalence of ED increases with age. It increases by 10% per year of age [1]; it increased from 2% in age group 18–38 years to 48% in the over 70 years and older [2]. In a large population-based study of 108,477 Australian men, the investigators reported that ED increased considerably with age [3]. Approximately one in five Australians over 40 years experiences ED [4].

Organic causes account for a large proportion of erectile dysfunction in the elderly than in the young. Organic causes include cardiovascular diseases, diabetes, renal failure, spinal cord trauma, complications of surgery and drug- or alcohol-induced dysfunction among others (Box 1). Smoking and

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_32

heavy consumption of alcohol can cause ED by damaging the nerves and arteries of the penis [5]. Cardiovascular diseases, hypertension, ischaemic heart disease and peripheral vascular disease are frequently associated with ED. Forty percent of the diabetic men aged 60 years or over had ED all the time [6]. Medications cause erectile problems in about 25% of clinic patients [7]. About 10–20% of patients on thiazide diuretic may be affected by ED [8]. Tricyclic antidepressants and monoamine oxidase inhibitors, benzodiazepines and selective serotonin reuptake inhibitors are known to cause erectile failure, decreased libido and ejaculatory problems [6]. Anabolic steroids either due to a direct effect on penis or by suppression of normal androgen production can cause ED [9]. Recreational drugs such as cocaine, heroin, amphetamines, marijuana, alcohol and tobacco can cause ED as they depress the brain's response to sexual stimulus [5] (Box 1).

Box 1 Risk Factors in Men

Cardiovascular disease
- Hormonal disorders
- Systemic disease
- Neurological disorders
- Localised conditions
- Psychosocial problems
- Drugs/alcohol/smoking

Radical prostatectomy and bowel or bladder surgery for cancer can injure arteries and nerves of the penis. Localised disease of the penis such as Peyronie's disease often interferes with erection. Lifestyle changes that contribute to cardiac diseases and vascular disease such as cigarette smoking and overweight can interfere with the functioning of the muscle cells of the penis. Psychogenic causes though less common are often related to a distinct precipitating event. ED in older men often with psychogenic component is usually secondary to an organic cause [10]. Stress, anxiety, feeling of guilt, low esteem, depression, fear of sexual failure, anxiety about sexual prowess and self-consciousness are associated with ED. Depression in men is associated with decrease in erectile capacity which may be associated with significant sexual dysfunction [11]. There may be a physical cause that makes the individual anxious which makes the problem worse. RhoA/Rho kinase plays an important role in the regulation of cavernous smooth muscle, and changes in this pathway can contribute to ED in patient subgroups such as diabetes and vascular disease [12]. In primary testicular failure, the testosterone level is low and luteinizing hormone (LH) is high and the prolactin level is normal, whereas in pituitary failure, testosterone and LH will be low [13]. A high prolactin level occurs in pituitary hyperfunction [13].

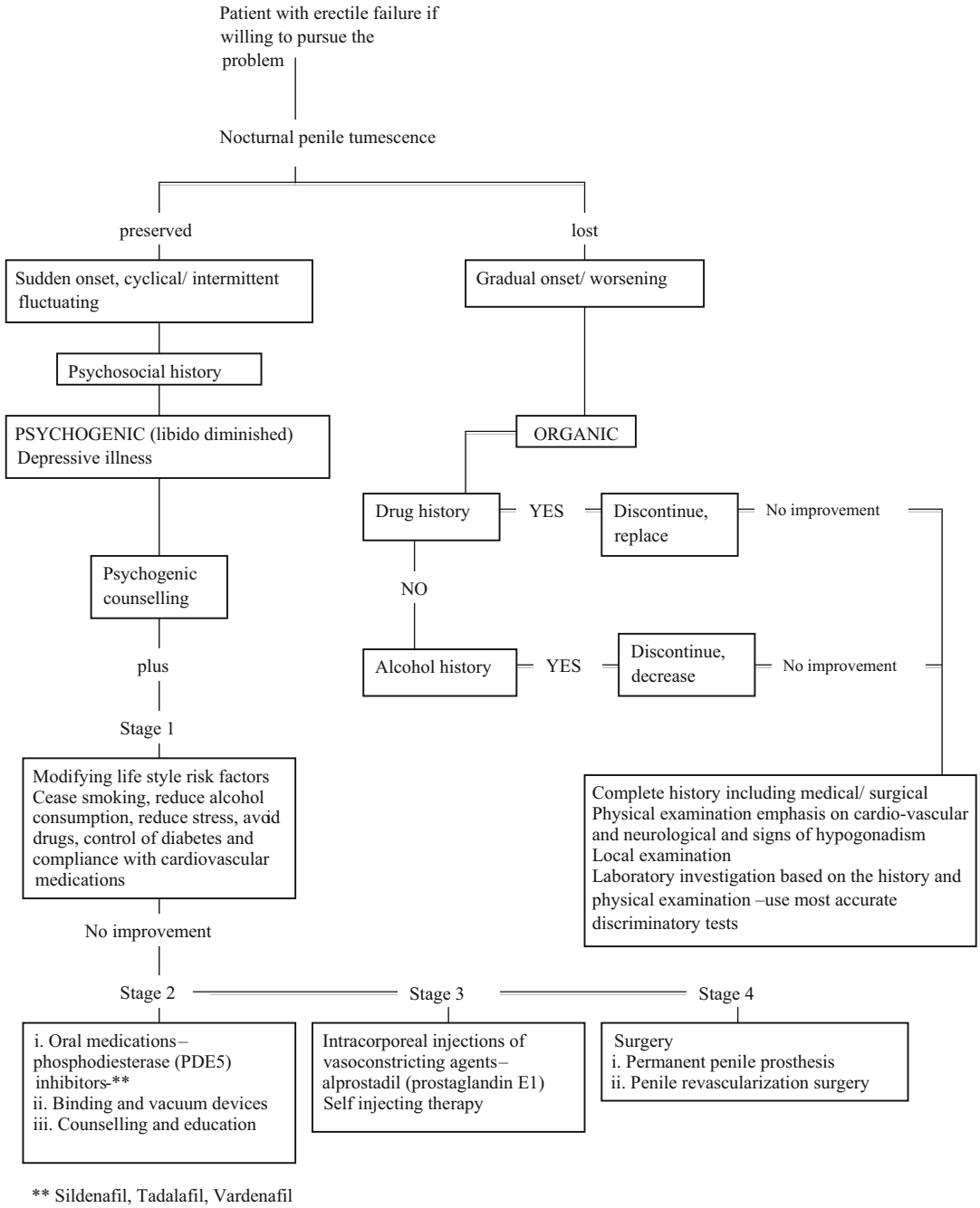
Evaluation

The clinician should appreciate the sensitivity of the situation and must avoid creating any unnecessary embarrassment and anxiety. The varied factors that may contribute to erection failure must be identified and addressed. The history must cover the causes that may interfere with erection:

i. Medical – cardiovascular disease, diabetes and neurological disorders – stroke
ii. Surgical – prostatectomy
iii. Pharmacological agents – antidepressants, beta-blockers and thiazides
iv. Drug-substance abuse – alcohol abuse, cocaine, etc.
v. Mental illness – depression and delusional disorders
vi. Lifestyle – sedentary, smoking and obesity

A thorough physical examination and measurement of nocturnal penile tumescence (NPT) are useful. NPT testing is particularly helpful to distinguish organic from non-organic causes [14]. Practically all men experience erections at night while at sleep, and they occur three to five times per night, and 80% of the erections occur during REM sleep [15, 16]. There are a number of ways to measure NPT ranging from simple devices (such as test strips resembling postage stamps which are pasted to the penis and separate at the perforations if erections occur) to more complex devices. These can

make a permanent quantitative record of the size, strength and duration of the erection. The Rigiscan is a tool of choice particularly for NPT and is considered the gold standard. Colour duplex ultrasound is a useful noninvasive method for studying the arterial blood supply



Algorithm 1 shows a step-by-step evaluation and management of a patient with erectile failure (Adapted from: Thase et al. [11], Kirby [14], UK patient. [18], Ende [19])

[17]. Algorithm 1 shows a step-by-step evaluation and management of a patient with erectile failure.

Management

There are several factors in the patient's ED which are amenable to several treatment modalities. Changes in the lifestyle, for example, increasing physical activity, quitting smoking and moderation in alcohol consumption, may be helpful.

Medications

Currently promising medications are available. The phosphodiesterase (PDE5) inhibitors (sildenafil, vardenafil, tadalafil) are effective in improving ED. Sildenafil is quick-acting, whereas tadalafil is longer-lasting. The newer ones are udenafil and avanafil. Cyclic guanosine monophosphate (cGMP) helps to maintain erection, and PDE5 normally breaks down the cGMP. The PDE5 inhibitors inhibit the conversion of cyclic guanosine monophosphate (cGMP) to GMP; therefore, more cGMP is available to prolong the vasodilatory effects of nitric oxide (NO) in smooth muscle cells within the corpus bodies of the penis. Impaired formation and action of NO is an important factor in the causation of ED [20].

PDE5 are safe in patients with a history of coronary artery disease (CAD) [21]. Analysis of clinical trials of the three PDE5 inhibitors did not show myocardial infarction or death rates different than that of placebo or different than the expected number for aged-matched population [22]. Several studies examined the effect of PDE5 inhibitors on the development of cardiac ischaemia in men undergoing exertion equivalent to or greater than achieved during sexual activity. These men had known coronary artery disease. None of the PDE5 inhibitors caused ischaemia or coronary vasoconstriction. Any person considered for PDE5 therapy however must undergo a thorough cardiovascular assessment.

Adverse effects: Vardenafil increases QTc in ECG. It is not recommended in congenital prolonged QTc interval and in patients in type 1A (quinine, procainamide) or type 3 (sotalol, amiodarone) antiarrhythmic agents. Caution is needed when administering any vasodilator drugs in patients with baseline hypertension, hypovolaemia, aortic stenosis and LV outflow obstruction [23]. Side effects include headache, flushing, visual changes with sildenafil and myalgia and back pain with tadalafil. Organic nitrates remain a contraindication.

Patients should be instructed to take the medication 30 min to 1 h before sexual activity. Sildenafil on a full stomach delays absorption. Sexual stimulation is required for the drug to work for sexual stimulation results in release of NO which is needed to 'prime the pump' of the biochemical pathway leading to erection [24]. In some patients with hypogonadism, testosterone may improve erectile function but should not be used in eugonadal men. Bromocriptine or similar drugs are usually used in hyperprolactinaemia. If medications are not helpful, other treatments include mechanical devices, penile injections, penile prosthesis and surgery.

Impact

Male erectile dysfunction has a significant impact on health-related quality of life [25]. It has considerable psychological and social effect [26] with marked effects on self-esteem and their relationships [27]. On an online survey, 62% of the partakers with erectile dysfunction reported reduced self-esteem, and 21% reported their relationship ended as a direct result [28]. Other feelings experienced by the men include a feeling of insecurity, anger and aggression, shame, guilt and afraid of being intimate with their partner [29]. The partners are often confused, frustrated and insecure about their partner's love or that he is having an affair, feeling of being unattractive and feeling of hopelessness [29] (Box 2).

Box 2 Key Points: Erectile Dysfunction

Erectile dysfunction is a common problem in general medical practice.

Organic causes account for a large proportion of erectile dysfunction in the elderly than in the young.

Ageing, hypertension, smoking, hypercholesterolaemia, diabetes [6] and structural changes in the penile issue conditions that are associated with reduced function of the endothelium can contribute to ED.

In the elderly, psychogenic cause is often secondary to an organic cause [10].

In the evaluation, nocturnal erections are important; it is lost in organic impotence.

There are several factors in the patient's ED which are several amenable treatment modalities. Changes in the lifestyle, for example, increasing physical activity, quitting smoking and moderation in alcohol consumption, may be helpful.

Currently promising medications are available. The phosphodiesterase (PDE) inhibitors (sildenafil, vardenafil, tadalafil) are effective in improving ED.

Caution is needed when administering any vasodilator drugs in patients with baseline hypertension, hypovolaemia, aortic stenosis and LV outflow obstruction [23]. Organic nitrates remain a contraindication.

GPs' role in men with erectile dysfunction is to perform a clinical assessment, treatment including counselling, appropriate referral and follow-up.

Multiple Choice Questions

1. The following are useful in the evaluation of organic impotence, EXCEPT:
   A. Measurement of nocturnal penile tumescence (NPT).
   B. Colour duplex ultrasound.
   C. Palpation of the penis for localised disease.
   D. The Rigiscan is not a tool of choice.
2. In the elderly, erectile dysfunction may be associated with the following, EXCEPT:
   A. In the elderly, psychogenic cause is often secondary to an organic cause.
   B. Ageing, hypertension, smoking, hypercholesterolaemia, diabetes and structural changes in the penile issue.
   C. Surgery radical prostatectomy and bowel or bladder surgery.
   D. Drinking alcohol occasionally.

MCQ Answers

1 = D; 2 = D

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Part VII

Neurological Disorders in the Elderly

The motor problems in Parkinson's disease (PD) can be preceded by several years by subtle clinical symptoms such as rapid eye movement sleep behavior and hyposomia during the prodromal period of PD. Part VII reviews Parkinson's with emphasis on the age of onset. Parkinson's disease usually begins in middle to late life (late-onset – LOPD). In about 5–10% PD begins before the age of 50 (early-onset – EOPD). There are some distinguishing features between both. MSA can cause combinations of parkinsonism, autonomic, pyramidal, and cerebellar symptoms. This section gives a concise account of the demographic, clinical and management of the disease. Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder. There is an association between frontotemporal dementia (FTD) and ALS. The disease is relentlessly progressive. Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease. Late-onset multiple sclerosis (LOMS) is defined as the first presentation of clinical symptoms occurring after the age of 50 years. The two groups "adult onset" (AOMS) and "late onset" (LOMS) defer in their demographic, clinical characteristics, disease course, and response to treatment. Peripheral neuropathy is less common in the old-old (>80 years) compared to the young-old (65–79 years), 25% vs. 46%. It may affect a single nerve or nerve root (axonopathy or radiculopathy). Diabetes and alcoholism are the most common causes of polyneuropathy in Australia. Guillain Barre syndrome (GBS) is the third most common. GBS has a bimodal age distribution, one peak in the young and another in the older population. GBS can be divided into demyelinating and axonal forms based on pathological and electrodiagnostic findings. Clinically and epidemiologically it is possible to recognize two subtypes of myasthenia gravis (MG): the early onset (EOMG) and the late onset (LOMG). Significant therapeutic progress has been made in the treatment of MG and introduction of new modalities especially immunosuppressive, immunomodulating drugs, plasma exchange, and thymectomy. Eiplepsy often develops for the first time in old age. In the elderly, cerebrovascular and neurodegenerative diseases are the leading causes of epilepsy. Periodic lateralizing epileptiform discharges (PLEDS) have been commonly associated

with cerebral infarction but also in other cerebral diseases such as encephalitis, tumor, and demyelinating diseases. Elderly individuals who have seizures must be carefully evaluated. Investigations should include neuroimaging. A common manifestation of epilepsy in the elderly is nonconvulsive status epilepticus (NCSE). Monotherapy is the main goal of epileptic treatment and majority can be controlled on a single agent.

Parkinson's Disease

36

Contents

Abstract

Parkinson's disease is a progressive disorder caused by degeneration of the dopaminergic neurons of the substantia nigra. Years before the substantia nigra compacta (SNc) and cortex are involved, there is pathological evidence of PD in the medulla oblongata, pontine tegmentum and olfactory bulb. The motor problems can be preceded by several years by subtle clinical symptoms such as rapid eye movement sleep behaviour and hyposmia during the prodromal period of PD. The striatonigral pathway plays a regulatory role in the system of positive and negative pathways that serve to modulate feedback from the thalamus to the motor cortex. This chapter reviews PD with emphasis on the age of onset. Parkinson's disease usually begins in middle to late life (LOPD). In about 5–10%, PD begins before the age of 50 (EOPD). There are some distinguishing features between both.

Keywords

Parkinson's disease · Glucocerebrosidase (GBA) gene mutations · Late-onset Pompe disease (LOPD) · Early-onset Pompe disease (EOPD) · Lewy bodies · Striatonigral pathway · Secondary parkinsonism

Introduction

Parkinson's disease is considered a movement disorder [1, 2]. In idiopathic Parkinson's disease, there is accumulation of alpha-synuclein in neuronal perikarya (Lewy bodies) and neuronal processes (Lewy neuritis) [3]. The majority of PD cases are sporadic, and about 10% are the rare familial forms, gene-linked encoding alpha-synuclein, parkin, dJ-1, PINK-1 and LRRK2 [4]. Glucocerebrosidase (GBA) gene mutations are now recognised as numerically the most important risk factor for PD [5]. Early-onset PD

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_42

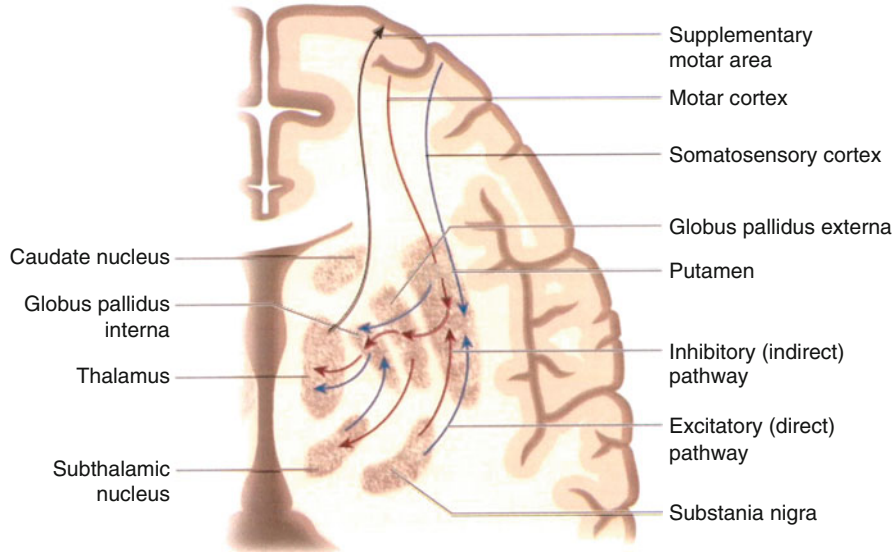


Fig. 1 Schematic diagram of direct and indirect pathways of the basal ganglia motor circuits. Direct pathway (*blue*) (D1). Projections from the caudate/putamen, GPi, thalamus to premotor cortex. Excitatory inputs from the substantia nigra and cortex to the putamen/caudate are also shown. Indirect pathway (*red*) (D2). Projections from the caudate/putamen, GPe, subthalamic nucleus, GPi, thalamus to motor cortex. GPe also receives excitatory input from the cortex and inhibitory from the substantia nigra. There is an excitatory input from the subthalamic nucleus to the GPi

with slower progression than the idiopathic disorder is produced by mutations in parkinsonism and results in loss of midbrain dopamine neurones [6].

In PD alpha-synuclein misfolds and forms intracellular inclusions called Lewy bodies which are the pathological hallmark of PD [7]. Several genes may be involved [8], and misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway play an important role in PD pathogenesis [9]. Accumulation of alpha-synuclein may be related to synaptic dysfunction in PD [10] and is brought about by either environmental or genetic factors [11] triggered by a chain of events resulting in dopaminergic neuronal death and dopamine depletion in the striatum which is the hallmark of PD [12]. Parkinsonian symptoms are believed to be due to abnormal synchronous oscillating activity within the basal ganglia [12] and play a vital role in the generation of the disease [13]. Loss of dopaminergic neurones in the midbrain [14] is commonly associated with dysfunction of the basal ganglia. Loss of dopaminergic inputs to the basal ganglia, that is, subthalamic nuclei and globus pallidus, results in increased oscillatory firing and synchronisation [15].

Increased knowledge and better understanding of the organisation of the basal ganglia in both health and disease have led to the hypothesis of direct and indirect pathways of the flow through the basal ganglia of cortical information [16] (Fig. 1). The internal basal ganglia circuits are controlled by several pre- and postsynaptic mechanism [1].

Clinical Manifestations

According to Braak et al. [8] long before the substantia nigra compacta (SNc) and cortex are involved even over years, there is pathological evidence of PD as defined by the presence of Lewy bodies in the medulla oblongata, pontine tegmentum and olfactory bulb. The onset motor problems can be preceded by several years by subtle clinical symptoms such as rapid eye movement sleep behaviour and hyposmia during the

Table 1 Shows the differentiation and similarities between early-onset and late-onset PD

	Early onset	Late onset
	<50 years	>50 years
Family history	More likely	Less likely
Clinical features		
Resting tremor	Frequent as initial symptom	Frequent
Rigidity, cramps	More common	Common
Bradykinesia	Frequent	Frequent
Gait difficulty	Frequent	More frequent
Posture instability		
Other		
Depression, anxiety	More likely	Less likely
Cognitive dysfunction	Progressed slowly	Impaired
Treatment-related side effects	More likely	Less so
Dyskinesia, dystonia		
Quality of life(QoL)	Poorer	Poor
Progression		

Information sources: Tang et al. [23], Bertucci et al. [24], Parkinson Disease Foundation [25], Mehanna et al. [26], and Fereshtehnejad et al. [27]

prodromal period of PD [17]. Parkinson's disease usually begins in middle to late life (LOPD). In about 5–10%, PD begins before the age of 50 (EOPD). There are some distinguishing features between both (Table 1). LOPD exhibited more often tremor at the beginning [18], and tremor is only present in half the number of patients with early onset. Rigidity and akinesia are more prominent with EOPD with rapid establishment of full-blown clinical picture and deterioration of the therapeutic efficacy of L-dopa [19]. The response to levodopa was greater and duration shorter in EOPD patients, and posture and gait symptomatology were less responsive in older patients [20]. Although the response to levodopa is significant, side effects are seen early [19], and this group has a greater proclivity to levodopa-induced dyskinesias and fluctuations as early as 6 months. LOPD patients are more susceptible to psychiatric complications [21]. The progression of the disease is slower with EOPD patients, but it is related more to the age of the patient rather than to the age of disease onset [22].

The early stages of PD may often be characterised by non-specific symptoms such as depression and fatigue, aching and tightness in the leg and arm, clumsiness of the hand, subtle decrease in mobility with less arm swing and flexed posture with difficulty in swallowing. The tremor may be intermittent. There is little difficulty in recognising idiopathic Parkinson's disease when it is well established. The combination of tremor, rigidity, bradykinesia and gait disorder is the classic syndrome of the idiopathic Parkinson's disease. This syndrome is not seen in any other neurological disorder. The difficulty may arise in some cases in differentiating it in the early stages of the disease, or when it presents with rigidity and bradykinesia, from other movement disorders. The tremor is present at rest, decreases with movement and disappears during sleep. It may involve the hand, jaw and feet. The rhythmic pronation and supination of the arm characteristically cause the 'pill-rolling' of the opposed thumb and fingers. The rigidity affects all muscles most markedly the trunk and neck. A cogwheel effect is often noted on passive movement of the extremities due to the combination of tremor and rigidity. There is slowness (bradykinesia) in the carrying out of voluntary movements. Flexion of the neck and trunk and the arms produces the distinctive posture with postural instability and falls. Posture and gait disorders are the least distinguishing of the presenting features. The 'mask-like' face is very obvious to the trained observer. The speech is dysarthric (monotonous, slow and low volume). The hand writing is micrographic, and there is drooling of saliva.

Differential Diagnosis

There are few conditions that may be confused with Parkinson's disease. Benign essential tremor is commonly mistaken for PD. Although the tremor is postural, this may be the initial and only sign of early PD causing difficulties in diagnosis. The patient with essential tremor would have had it for several years, and there is often a family history. The tremor worsens with skilled

acts and there is often a head tremor and there is no rest tremor, rigidity or bradykinesia.

The clinical presentation of drug-induced parkinsonism is exactly the same as classic PD and clinically indistinguishable. The common drugs which are culpable are the older antipsychotics, for example, haloperidol and antiemetics such as prochlorperazine and metachlorpropamide. A careful history must be taken in patients who present with Parkinson's. A few neurodegenerative disorders like progressive supranuclear palsy, nigrostriatal degeneration, MSA-P syndrome and other conditions like normal pressure hydrocephalus and multiple cerebral infarctions may mimic PD. Box 1 shows the clinical features differentiating them from PD.

Box 1 Clinical Features of Parkinson-Plus Syndromes

Absence of typical tremor
Early onset and predominance of unsteady gait and postural defect and falls
Atypical rigidity and dystonic features
Early onset of dementia
Abnormal deep tendon reflexes and plantar responses
Early onset of bladder dysfunction
Impaired extraocular movements
Very poor response to anti-parkinsonian treatment
Rapid progression of disability
Early occurrence of postural hypotension even prior to treatment

Progressive supranuclear palsy is a progressive disease with stiffness, unsteady gait, falls and visual complaints. Vertical downward gaze is lost and axial more than appendicular rigidity, dysarthria and slow mentation (subcortical dementia) with poor response to levodopa. In nigrostriatal degeneration, there are bradykinesia, unsteady gait, dysarthria, orthostatic hypotension and rigidity. Mentation is intact and response to treatment is poor. Dyspraxic gait, incontinence and dementia are the classical triad of normal pressure hydrocephalus. The gait is short and shuffling or 'magnetic' (like walking in mud). With multiple cerebral infarctions, there are increased muscle tone, some degree of bradykinesia and gait disorder, and the diagnosis is based on the presence of focal cerebral dysfunction. The clinical features of Parkinson-plus syndromes differ from that of idiopathic Parkinson's disease as in Table 2.

Management of Parkinson's Disease

Most people with early PD are treated by the primary care physician, and it is important that the primary care physician should have an understanding of what happens in Parkinson's disease. However, initially to confirm the diagnosis and later with increasing severity and complications, referral to a neurologist and co-management is necessary.

The decision to initiate treatment depends on several factors, for instance, age of the patient at the onset of the disease, degree of disability, patients' expectations and social and occupational demands, and hence treatment must be individualised. Evaluation of the patient can be quantitative or qualitative. The former is often time-consuming, but the latter is relatively simple and rapid. There are a number of clinical rating scales available, but the one widely used is the Unified Parkinson's Disease Rating Scale (UPDRS) which assesses 42 items on a four-point score system to determine the patient's mental status, activities of daily living, motor function and complications of therapy [28].

Levodopa is still considered the most effective drug for the treatment of Parkinson's disease even though long-term therapy is associated with motor complications that can be as disabling as the disease itself. Patients encounter symptoms of severe involuntary movements and the 'switching-off' phenomenon possibly due to abnormal pulsatile delivery of the dopamine. Levodopa-induced dyskinesia may be reduced with non-selective *N*-methyl-D-aspartate antagonist amantadine and fipamezole (noradrenergic alpha2A antagonism) can potentially reduce dyskinesia.

To improve motor outcomes, dopamine agonists (pramipexole, ropinirole, rotigotine), monoamine

Table 2 Differential diagnosis of Parkinson's disease

Disease	History and clinical manifestations	Treatment
Idiopathic Parkinson's disease	Gradual onset, resting tremor, rigidity (affecting peripheral more than distal) gait disorder, bradykinesia	Levodopa, non-ergot agonist, COMT inhibitor, selegiline
Drug-induced parkinsonism	Exposure to drugs such as haloperidol findings indistinguishable to idiopathic Parkinson's disease	To cease drug
Progressive supranuclear palsy	Stiff, unsteady gait, falls, visual disturbances, (vertical gaze to all gaze lost), axial and appendicular rigidity, slow mentation cervical dystonia	Trial with levodopa physical therapy
Multiple cerebral infarctions	Multiple strokes, stepwise progression focal findings, asymmetric motor or sensory, infarcts on CT, periventricular lucencies	Aspirin, risk factor control blood pressure
Binswanger's disease	Rigidity, slowing with pseudobulbar palsy. Neuroimaging-lacunes, infarcts in the white matter	As above
Normal pressure hydrocephalus	Dyspraxic gait, urinary incontinence, dementia with frontal lobe features	Consider ventriculoperitoneal shunt
Striatonigral degeneration	Unsteady gait, dysarthria, orthostatic hypotension, rigidity, mentation intact	Response to treatment poor
Multisystem atrophy	Parkinsonism, autonomic system dysfunction (orthostatic hypotension) cerebellar and pyramidal signs	Levodopa trial, control blood pressure

oxidase B inhibitors (rasagiline) and catechol-O-methyltransferase inhibitors (entacapone) can provide continuous oral delivery of dopaminergic stimulation [29]. The dopamine agonists are longer acting, may be neuroprotective and slow the progression of the disease [30, 31]. Dopamine agonists are less likely to produce long-term motor complications but are not as effective as L-dopa. They can be used before going on to L-dopa, except in those aged over 70 years with significant disability. Neither bromocriptine nor pergolide is used anymore because they are ergot alkaloids and have significant side effects. The most important of these are mediastinal and cardiac (valvular) fibrosis. Cabergoline, another ergot dopamine agonist, also causes fibrotic reaction in the cardiac valves. It is used as a monotherapy in PD in the early phase. It could be used in combination with L-dopa and decarboxylase such as carbidopa in progressive phase of PD. Patients on cabergoline should be screened regularly with X-ray of chest, electrocardiogram and renal function tests.

Another class of medications helpful in treating PD are the non-ergot dopamine agonists, oral ropinirole, Requip, pramipexole, Mirapex, and the rotigotine transdermal patch. They act like levodopa and are useful in the early stages of the disease and an option for an initial treatment for younger patients with mild to moderate symptoms [32, 33]. These can be used in combination with levodopa and may reduce the amount of 'off time' when patients have difficulty with motor activity. Both however have been linked with new onset of compulsive behaviours such as gambling and hypersexuality. Rotigotine, a non-ergot dopamine agonist, delivers a more regular dopamine stimulation through a transdermal patch, releasing approximately 2 mg per 24 h. It is indicated as monotherapy or in combination with existing levodopa therapy in patients with early to advanced disease.

Rasagiline is the newer drug and is preferred by many to selegiline. It has been extensively used in Europe. There are reports that rasagiline slows progression of the disease and improves control of motor fluctuations in advanced disease and in the treatment of motor symptoms. It may be useful in early PD and is a potent selective irreversible MAO-type B inhibitor. It impairs thinking and reactions and can produce unexpected drowsiness, and motor vehicle accidents have occurred as a result. Certain foods and beverages that are high in tyramine should be avoided.

The anticholinergics are most effective in those with significant tremor, but their side effects limit

their use especially in the elderly. Muscarine M4 cholinergic antagonists are useful in the treatment of PD tremor, but tolerability is often poor [34]. Other options include clozapine, antidepressant mirtazapine and 5-HT2A [34]. The COMT inhibitors decrease the degradation of levodopa thereby reducing the end-of-dose wearing-off effect. However, it has been associated with fatal hepatotoxicity and requires close monitoring with liver function tests. Entacapone (COMT-I) in combination with L-dopa preparations (Stalevo) smooths the delivery of dopamine to the brain thus reducing the amount of time spent 'switched off'. Potential side effects include nausea, dizziness, diarrhoea and involuntary movements. Some patients especially those with early onset show earlier and more often severe motor fluctuations and dyskinesias. In these patients, surgery or alternate routes of administration of dopaminergic medications have been shown to reduce the motor fluctuations. Apomorphine is an injectable form of dopamine agonist and has been shown to reduce daily off time of about 50% and maintained for long-term benefit [35]. In advanced Parkinson's disease, more stable plasma levels can be achieved by DUODOPA which is a combination of levodopa and carbidopa in the form of a gel and is administered by a portable pump directly into the duodenum through a tube inserted in a percutaneous endoscopic gastrostomy (PEG). The commonly used drugs are shown in Table 3.

Co-enzyme Q-10 is being used "off-label" as a neuroprotective agent to slow progression. It is an antioxidant sold as a dietary supplement and is also involved in mitochondrial processes. Over recent years, there has been a renewed interest in surgery, and this has largely been due to the limitations of medication. Chronic levodopa-associated motor fluctuations and dyskinesias, the variable response to tremors and advances in stereotactic surgery are some of the reasons for this shift.

In moderate to severe PD patients, where drug treatment was ineffective, and in those with certain drug reactions, Wu et al. [40] have listed the following options, namely, (1) striatum stereotactic pallidotomy, (2) stereotactic technique of deep brain stimulation, (3) stem cell implantation via brain stereotactic surgery, (4) subarachnoid stem cell implantation via lumbar puncture and (5) gene-targeted stem cell implantation in subarachnoid via lumber puncture. Surgery in PD is carried out on structures that are responsible for the modification of movements, e.g. globus pallidus, thalamus and subthalamic nucleus. Currently the more important surgical techniques are lesioning (pallidotomy, thalamotomy) and chronic deep brain stimulation (DBS) especially of the subthalamic nucleus [29]. There is considerable reduction in the symptoms, and the patients are able to reduce their medications.

Pallidotomy has been replaced largely by thalamotomy. Thalamotomy is believed to relieve tremor more consistently than pallidotomy with lower rate of symptom recurrence and found to be effective in relieving rigidity and drug-induced dyskinesias. It is usually performed in patients under 65 years with normal memory and intellectual functions. Thalamotomy is rarely done today and largely replaced by deep brain stimulation. Deep brain stimulation (DBS) is considered the surgical treatment of choice for PD and is effective in the right situation. There is less destruction of brain tissues than other surgical methods which is effective and safe. Stimulation of the ventral pallidum relieves rigidity, and the ventrolateral nucleus of the thalamus abolishes tremor. Stimulation of the STN and GP may reduce tremor, on-off motor fluctuations and abnormal movements (dyskinesias) induced by long-term use of levodopa. The Algorithm 1 addresses the problem of management of idiopathic Parkinson's disease.

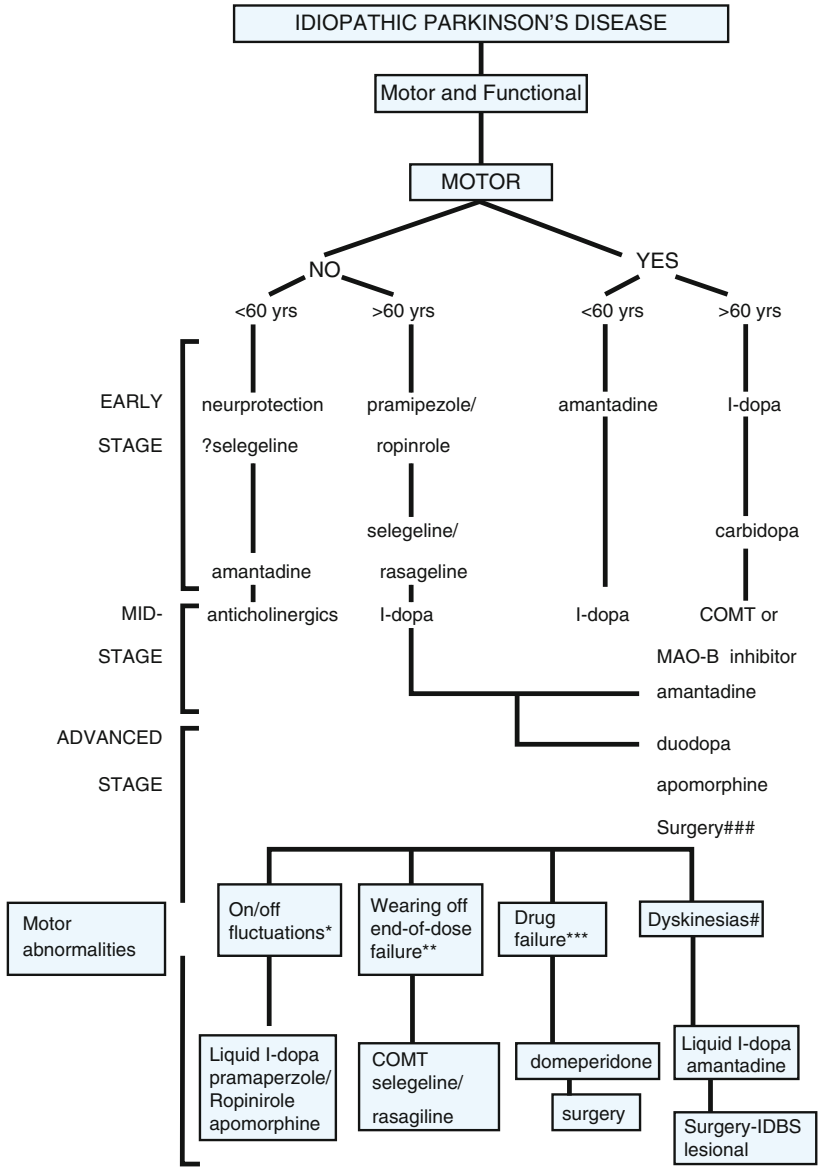
The motor symptoms of PD are well recognised, but the non-motor symptoms have been neglected for years. There is now an increase in awareness that they are equally important in the effectual management of the patient with PD. These symptoms may sometimes be present before the diagnosis of PD but inevitably emerge as the disease progresses [41]. They are quite disabling and contribute to reduced quality of life, increase in caregiver burden and institutionalisation and shorten life expectancy [41].

Depression is the most commonly occurring non-motor symptom in PD and manifests

Table 3 Commonly used drugs in Parkinson's disease

Drug	Mode of action	Side effects	Starting dose
I. Increase dopamine levels			
Levodopa/carbidopa	Precursor decarboxylase inhibitor	Nausea, vomiting dizziness, orthostatic hypotension, hallucinations, cardiac irregularities, mental changes, confusion, abnormal movements, unusual sexual urges	25/100 mg tid
II. Stimulate dopamine receptor			
Ergot dopamine agonists			
Bromocriptine[a,b]	Dopamine agonist receptor stimulation	Nausea, vomiting, hallucinations, hypotension, confusion	1.25 mg bd
Pergolide[b]	Stimulates D1 and D2 dopamine receptors	Hallucinations, fibrosis of cardiac valves, retroperitoneal and pulmonary fibrosis psychiatric symptoms	0.05 mg at bedtime
Cabergoline	Stimulate\d D2 receptor	As above	0.5 mg daily maximum dose 3 mg
III. Non-ergot dopamine agonists			
Pramipexole	Dopamine agonist	Compulsive behaviours, sleep attacks, impulse control disorders[c]	0.125 md tds (max:4.5 mg)
Ropinirole	Dopamine agonist	As above	0.25 mg tds (max:3 mg)
Rotigotine	Dopamine agonist 2 mg/ 24 h	As above	Transdermal patch
Apomorphine	Dopamine agonist	Severe nausea	As subcutaneous injection
IV. Inhibit dopamine metabolism			
Tolcapone[d]	COMT inhibitor	Nausea, vomiting, confusion, insomnia orthostatic hypotension	100 mg tid (adjunct to L-dopa)
Entacapone			200 mg daily (adjunct to dopa
Stalevo (COMT-I entacapone + carbidopa)		Involuntary movements	Diarrhoea, dizziness, nausea
V. MAO inhibitor			
Selegeline[a]	MAO-B inhibition	Headache, insomnia sweating	5 mg bd
Rasagiline	MAO-B inhibition	Impairs thinking, reactions	0.5 mg daily
VI. Blockade of NMDA receptor from peripheral neurons		Confusion, nausea hallucinations leg oedema, livedo reticularis	100 mg bd
VII. Anticholinergics[e]			
Trihexyphenidyl	Anticholinergic	Dry mouth, confusion,	1 mg daily
Benztropine		Urinary retention,	0.5–1.0 mg daily
Procyclidine		Constipation, narrow angle glaucoma prostatism, hallucinations	2.5 mg tid

Information sources: DeMaagd and Philip [36], Chen and Swipe [37], Perez-Lloret and Rascol [38] and Jenner [39]
[a]Dopamine agonists, selegiline, amantadine because of their CNS effects – used with caution in elderly patients
[b]Neither is used anymore because of the risk of cardiac valve and mediastinal fibrosis. Replaced by pramipexole and ropinirole
[c]Related to phenomenon as dopamine dysregulation syndrome [36]
[d]Fatal liver damage had occurred with tolcapone
[e]Produce confusion and hallucinations in the elderly



Algorithm 1 Addresses the Problem of Management of Idiopathic Parkinson's Disease. *Unpredictable abrupt fluctuation in motor state between undertreated and over-treated states, **Shorter duration of benefit after L-dopa, ##After several years of levodopa therapy, ***Beginning of dose deterioration, !DBS = deep brain stimulation, #Drug and disease related, ###Globus pallidus internal-segment pallidotomy, deep brain stimulation and nigral transplantation hold promise for the future

somewhat differently from the depression in otherwise healthy people. According to Braak et al. [42], several areas outside of substantia are involved. The PD group has been reported to have less pleasure, less sadness, less guilt and less energy [43]. Other non-motor symptoms include cognitive disturbances, disorders of sleep, psychiatric symptoms, such as hallucinations, and autonomic disturbances. Even in early stages of the disease, several neuropsychological deficits such as defective use of memory stores, impaired behavioural regulation and planning

tasks have been recognised [44]. Dementia is a late development in PD. Some of the non-motor symptoms such as sleep problems, genitourinary symptoms, pain, constipation and diarrhoea can be improved with available treatment [41] (Boxes 2, 3 and 4).

Box 2: Nonmotor Symptoms of PD

Psychiatric
- Mood disorders-depression
- Anxiety/panic attacks
- Hallucinations, paranoia
- Impulse control disorders
- Apathy

Cognitive disturbances
- Slowing of voluntary and involuntary response
- Dementia

Sleep disorders
- REM sleep disorder
- Daytime somnolence

Sensory impairment
- Autonomic disturbances
- Erectile dysfunction
- Constipation
- Gastric dysmobility

Information sources: Chadhuri et al. [41]; Postuma et al. [45]; Simuni T, Sethi [46]; Truong et al. [47].

Box 3 Key Points: Clinical Expression of Parkinson's Disease

PD usually begins in middle to late life (late onset), and in 5–10%, it begins before the age of 50 years.

The early stages of PD is characterised by non-specific symptoms.

In about 5–10%, PD begins before the age of 50 (EOPD). There are some distinguishing features between both.

The combination of tremor, rigidity, bradykinesia and gait disorder is the classic syndrome of idiopathic PD.

Box 3 Key Points: Clinical Expression of Parkinson's Disease (continued)

The difficulty in diagnosis may arise in some cases in the early stages or when it presents with rigidity and bradykinesia from other movement disorders.

The non-motor symptoms in PD are equally important.

The decision to treat depends on several factors, for instance, age of the patient at time of onset, degree of disability, patients expectations and social and occupational demands.

Box 4 Key Points: Treatment of Parkinson's Disease

L-Dopa is the most effective drug, but patients may encounter severe involuntary movements and the 'switching off'. Dopamine agonists less likely to give rise to side effects but are less effective. Neither bromocriptine nor pergolide is used now because they are ergot alkaloids.

Another class of non-ergot dopamine agonists is ropinirole and pramipexole. Both have a new set of side effects: compulsive behaviours, gambling and hypersexuality.

In recent years, there is a renewed interest in surgery-surgical techniques – lesioning (thalamotomy and pallidotomy) and deep brain stimulation (DBS). Stimulation of the ventral pallidum relieves rigidity, and the ventrolateral nucleus of the thalamus abolishes tremor.

Impact

As the disease progresses, patients with PD experience worsening of their physical manifestations such as developing swallowing difficulties, walking difficulties and difficulty in communication,

becoming cognitively impaired and developing behavioural problems and autonomic problems such as sexual dysfunction and lightheadedness, amongst others [48]. PD continues to be an unrelenting progressive disorder resulting in severe disability despite progress in newer pharmacological treatments [29]. PD can affect many aspects of the person's daily life and negatively affect their social interactions. They develop psychosocial issues which affect their QoL. It adversely affects motor functioning resulting in disability and impact on QoL [49]. In a study of 95 patients with PD with regard to the impact of the disease on functional condition, the researchers found that impairment occurred in three categories, 'walk', 'social interaction' and clarity of mind', and the highest percent was in 'motor control' and least in 'emotional stability' [49]. PD can affect severely the health-related quality of life (HR-QoL) [50] in both patients and carers [49] as the disease progresses. Patients with early-onset and late-onset PD have different clinical profile and hence have different impact on their lives. There is a higher prevalence of mood disorder and anxiety in individuals with Parkinson's disease which play an important role to worsen quality of life in both groups [27]. Patients with PD have a high likelihood of increasing dependency, premature ageing and reduced occupational performance [27]. PD markedly reduces HR-QoL of patients and caregivers and places a tremendous economic burden on society. The economic costs include direct health-care costs and indirect costs (lost worker productivity) [51], and the economic costs of PD are high particularly for patients in the advanced stages and with motor complications [52].

Multiple Choice Questions

1. The following in Parkinson's disease are true, except:
   A. Degeneration of the dopaminergic cells in the substantia nigra results in the dysfunction of the striatonigral-thalamic outflow.
   B. Dopamine is not bound to the postsynaptic receptors and inactivated by binding to the autoreceptors and is also inactivated by enzymes monoamine oxidase type B (MAO-B) and catechol-O-methyltransferase (COMT).
   C. The intraneuronal enzymes required for dopamine synthesis are diminished.
   D. It is a pyramidal disorder.
2. The following in Parkinson's disease (PD) are true except:
   A. In PD there are scattered neurons containing eosinophilic inclusions known as Lewy bodies which are the hallmark of the disease.
   B. Age of onset is between 60 and 70 years.
   C. The non-motor symptoms of PD are not important.
   D. The decision to treat does depend on factors such as age of the patient at onset, degree of disability and patient's expectations, amongst others.
3. The following management options in PD are true except:
   A. L-Dopa is most effective.
   B. Dopamine agonists, bromocriptine and pergolide, are not used anymore because they are ergot alkaloids.
   C. Non-ergot dopamine agonists such as ropinirole and pramipexole cannot be used in combination with L-dopa.
   D. Side effects of ropinirole and pramipexole are a new set of compulsive behaviours such as gambling and hypersexuality.
4. The following statements relating to PD are true, except:
   A. Presently the more important surgical interventions are lesioning (thalamotomy) and deep brain stimulation.
   B. Stimulation of the ventral pallidus abolishes tremor.
   C. Stimulation of the ventrolateral nucleus of the thalamus relieves rigidity.
   D. Deep brain stimulation is ineffective and unsafe.

MCQ Answers

1 = D; 2 = C; 3 = B; 4 = D

Extended Matching Questions (EMQ)

1. Gastrointestinal effects are common to all dopaminergic medications, but there are side effects which are characteristic of certain drug types.

Given below are the side effects. Chose the appropriate drug type to match the side effects.

A. Ergoline dopamine agonist (bromocriptine, cabergoline, pergolide)
B. Levodopa
C. Non-ergoline dopamine agonist (pramipexole, ropinirole, rotigotine, apomorphine)
D. Entacapone (COMT)
E. MAO-B inhibitor (selegiline, rasagiline)
F. Anticholinergic

Side effects

1. Discoloration of urine
2. Somnolence, oedema, compulsive behaviours(gambling, hypersexuality)
3. Pleuropulmonary fibrosis, effusions, retroperitoneal fibrosis
4. Cognitive, psychiatric and insomnia
5. Hypotension, 'wearing off', dyskinesias
6. Cognitive Effects

EMQ Answers

1 = D; 2 = C; 3 =A; 4 = E; 5 = B; 6 = F

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Multisystem Atrophy (MSA)

37

Contents

Abstract

MSA can cause combinations of Parkinsonism, autonomic, pyramidal and cerebellar symptoms. MSA-A is now the term used for Shy-Drager syndrome, MSA-C if cerebellar symptoms predominate and MSA-P if Parkinsonian features predominate. The aetiology is uncertain although recently it has been attributed to a human prion composed of the alpha-synuclein protein. This chapter gives a concise account of the demographic, clinical characteristics and management of the disease.

Keywords

Multiple system antrophy · Parkinsonism · Shy-Drager syndrome · Autonomic dysfunction · Antecolis · Myotonic jerks

Introduction

Multisystem atrophy (MSA) can cause combinations of Parkinsonism, autonomic, pyramidal and cerebellar symptoms. All four characteristics occur in the vast majority of patients with MSA but with considerable variation with regard to specific symptoms, and any one of the four could predominate.

Symptomatology

It is Parkinsonism that commonly brings the patient with MSA to medical attention. In early stages, there are postural instability that is common [1] and unexplained falls and with progression the absence of tremor, severe early autonomic dysfunction, symmetrical involvement and lack of response to dopaminergic treatment that distinguishes MSA from idiopathic Parkinson's disease. Cerebellar signs together with tremors which are irregular and jerky, myotonic jerks and dystonic and distal contractures strongly suggest MSA. Cerebellar signs are seen in about 50% of cases [2]. Some have what is referred to as antecolis where the neck flexes forward on to the chest, and this may affect breathing, swallowing, speech and maintaining eye contact [3].

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_41

As the disease progresses, pyramidal, cerebellar and speech deficits gradually appear with excessive snoring or inspiratory stridor during the night, and later tracheostomy may be indicated [4]. The average survival time after initial diagnosis is 10 years, and patients usually die of an intercurrent illness. All patients with MSA die from disease-related events and most commonly sudden death and infections [5]. It affects men twice as often as women. Many are severely disabled within 5 years, and more than 40% become wheelchair bound. They become mute, but intellect and awareness are intact.

Rapid disease progression and shorter survival were seen in patients who had early involvement of autonomic function [6]. Another study found that the interval between initial symptoms to combined motor and autonomic dysfunction can predict functional deterioration and survival [7]. Autonomic dysfunction includes postural hypotension with syncope, impotence urinary and faecal incontinence [1].

Management

There is no cure. A recent study demonstrated that autologous mesenchymal stem cell therapy delayed the progression of the neurological deficits with functional improvement [8]. Management is symptomatic and targets the autonomic failure and Parkinsonism [9]. Salt supplements, florinef (fludrocortisone) and midodrine, are used in treatment autonomic dysfunction [1], and in MSA midodrine is said to work better in the orthostatic hypotension as the postganglionic sympathetics are retained [10] in MSA. There should be a multidisciplinary approach, and managing all symptoms may be unrealistic, and the main aim is to improve quality of life [3].

Impact

MSA is a progressive neurodegenerative disorder for which there is no cure. MSA can cause combinations of Parkinsonism, autonomic, pyramidal and cerebellar symptoms. In an analysis of 230 Japanese patients with MSA, the investigators found the median intervals from onset to aid requiring walking, wheelchair and bedridden and death to be 3, 5, 8 and 9 years, respectively [7] They further found that progression and survival of MSA involve several factors but more importantly the interval from initial symptom to combined motor and autonomic dysfunction [7]. Some of the problems encountered in patients with MSA and worsening as the disease progresses are speech and communication, swallowing, bladder and bowel problems, postural hypotension [7], mobility, mood and behaviour (Box 1).

Box 1 Key Points Multisystem Atrophy

In the early stages, there are gait instability and unexplained falls [1], and with progression there is absence of tremor and severe autonomic dysfunction.

They become mute but intellect and awareness remain intact.

Rapid disease progression and shorter survival were seen in patients who had early involvement of autonomic function [6].

Usually die suddenly and from infections [5].

Treatment is symptomatic and to ensure quality of life [9].

Salt supplements, florinef and midodrine, are used in treatment autonomic dysfunction [1].

Multiple Choice Questions

1. The following are true of multiple system atrophy (MSA) except:
   A. MSA can cause a combination of Parkinsonism, autonomic, pyramidal and cerebellar symptoms.
   B. MSA-A is now the term used for Shy-Drager syndrome.
   C. The hallmark of the disease is the widespread accumulation of Lewy bodies.
   D. Many patients with MSA are initially diagnosed as Parkinson's disease.

2. The following are true of multisystem atrophy (MSA) except:
   A. The average of onset of the disease is around 50 years.
   B. Intellect and awareness deteriorate as the disease progresses.
   C. Many become disabled in 5 years.
   D. Management is symptomatic.

MCQ Answers

1 = C; 2 = B

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Motor Neurone Disease

38

Contents

Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder. It affects both upper and lower motor neurons and is characterised by a progressive degeneration and death of the anterior horn cells, cortico-spinal tracts and/or bulbar motor nuclei. The cause is unknown. There is an association between frontotemporal dementia (FTD) and ALS. ALS commonly occurs between the ages of 40 and 60 years, and males are affected more than females. The disease is relentlessly progressive. The median life span is about 4 years. Most with ALS will die from respiratory failure. Symptoms of bulbar involvement usually imply a rapid course usually with survival of a year. There is no cure, and medical care is mainly palliation and involves a multidisciplinary approach.

Keywords

Motor neurone disease · Amyotrophic lateral sclerosis · Frontotemporal dementia (FTD) · Riluzole · El Escorial criteria · Awaji criteria

Introduction

The term motor neurone disease (MND) encompasses a group of disorders that result from degeneration of the motor neurons in the brain and/or spinal cord. Annual incidence is 2 cases per 100,000 and prevalence 5–7 per 100,000 [1]. In different population without manifesting a distinct geographical pattern, the incidence rate varied between 66 and 2.4 per 100,000 persons per year [2]. In the UK, the crude rate for MND was 3.1 persons per year in women and 4.3 in men [3]. In Scotland, the annual standardised incidence was 2.40 per 100,000 [4], and in Italy the annual crude rate was 2.9 per 100,000 [5].

Clinical Manifestations

The earliest symptoms are muscle cramps, twitching, stiffness and wasting in one or more limbs. ALS patients have signs and symptoms of both lower and upper motor neurone damages.

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_37

The disease is relentlessly progressive [6]. As the disease progresses, muscle wasting becomes generalised with brisk tendon jerks despite the muscle atrophy. The more important signs in ALS are that resulting from involvement of the bulbar motor nuclei and fasciculations in the tongue, palate and face with an exaggerated jaw jerk, speech becomes slurred and nasal, and communication becomes difficult. The tongue should be examined while within the mouth and relaxed. The protruded tongue may show a fine tremor which can be mistaken for fasciculations. Involvement of the thenar and first interosseous muscles with sparing of the hypothenar muscles referred to as 'split hand' is specific for motor neurone disease [7, 8]. Patients with ALS have difficulty in swallowing and chewing with a risk of choking. As the disease progresses, patients have difficulty standing, walking and using the arms and hands. Weakness of the respiratory muscles leads to dyspnoea.

ALS does not affect memory, intelligence and personality which are largely preserved, so are the senses of taste, smell, sight, hearing and touch. They maintain control of gaze and that of bladder and bowel functions. More recently a spectrum of cognitive deficits have been described such as apathy, mood changes and disinhibition [9] and a small minority progressing to FTD [10]. The differential diagnosis includes conditions that involve the spinal cord and nerve roots, as in cervical spondylosis provided there is no bulbar involvement, other disorders with multiple root compressions with lower motor neurone findings and spinal cord compression with upper motor neurone findings. The diagnosis of ALS remains a clinical one [11], but laboratory testing may be used to exclude other diseases and to confirm the diagnosis [12]. The electrodiagnostic studies include nerve conduction and electromyography which are useful in confirming ALS and for excluding other conditions that may resemble ALS [13]. Ultrasound is useful in detecting fasciculations. The electromyogram is most useful showing fasciculations, fibrillations and giant motor units even in the unaffected limbs with a drop-out of motor unit potentials. It should show evidence of muscle denervation in three extremities or in one extremity and bulbar muscles. Diagnostic tests are necessary when the patient has pure LMN disease so that asymptomatic UMN can be detected. Transcranial magnetic stimulation is useful in detecting cortical motor dysfunction. Measurement of the motor conduction time from the cortex to muscle by magnetic stimulation may show slowing. High-resolution MRI allows visualisation of the pyramidal tracts, and atrophy or demyelination may be seen. In some types of familial ALS, genetic testing can identify gene defects [12].

The revised El Escorial criteria (EEC) [14] was considered the gold standard for the diagnosis of ALS and has been based on the presence of 'A criteria' in the absence of 'B criteria'. The former includes lower motor neurone degeneration (LMN) as appraised by clinical, electrophysiological or neuropathological findings together with evidence of upper motor neurone (UMN) degeneration by clinical assessment and further includes progressive dissemination beyond the typical nerve supply areas [15]. The 'B criteria' requires that the degeneration of LMN and UMN should not be typical findings of other diseases and the findings on imaging studies explain the clinical symptoms [15]. It has been criticised that it permits the diagnosis only in the advanced stages [15], and a new criteria had been suggested, the Awaji criteria [16]. The essential difference between the two criteria being the Awaji criteria regards fasciculations with chronic neurogenic EMG changes in the clinical context as a sign of 'active denervation' [17].

The median life span is about 4 years, but the range of survival is from a few months to some decades, and most with ALS will die from respiratory failure. Symptoms of bulbar involvement usually imply a rapid course usually with survival of a year.

Management

There is no cure [17], and medical care is mainly palliation and involves a multidisciplinary approach, with a team of healthcare professionals, rehabilitation techniques and supportive care for patient and family. The aim is to prevent complications and improve quality of life [6]. The multidisciplinary approach has shown improvement in the quality of life [18, 19]. The only drug approved by the FDA in the USA for ALS is riluzole, a membrane stabiliser [10]. Its benefit is

limited and has shown modest prolonged survival [3]. Clinical follow-up by the primary care physician of ALS patients with its multiple symptoms and signs that differ in presence and severity among patients is an involved and arduous undertaking (Box 1). Transplantation of mesenchymal stem cells in patients with ALS and multiple sclerosis is said to be clinically feasible and induces immediate immunomodulatory effects [20].

Box 1 Check List for Primary Care Physician
Evaluation of

Mobility – stand, walk, get in and out of bed, use of arms and hands

Communication – speaking

Swallowing – risk of choking, loss of weight due to decreased intake

Difficulty in breathing – to count up to 20 without a pause, risk of aspiration

Stiff muscles (spasticity)

Impact

ALS an adult-onset neurodegenerative disorder is incurable, and only symptom treatment is available. Death occurs in 3–5 years from the time of diagnosis and is due to respiratory failure [21]. Respiratory muscle function is a strong predictor of quality of life [22] and survival [23]. Care in a multidisciplinary clinic had a better prognosis compared to general neurologic clinic [19], and patients had a better quality of life [24]. Van Der Steen et al. [24] examined the effect of treatment in a multidisciplinary ALS treatment centre compared to general care with a view to the costs and found the costs to be identical. Weight loss is a common occurrence in patients with ALS due to dysphagia or to factors not fully understood and has an impact on the quality of life [25] (Box 2).

Box 2 Key Points. Motor Neurone Disease
The other disorders in the group apart from amyotrophic lateral sclerosis

(ALS) include progressive bulbar palsy, progressive pseudobulbar palsy, progressive muscular atrophy, progressive lateral sclerosis, spinobulbar muscular atrophy and post-polio syndrome.

ALS commonly occurs between the ages of 40 and 60 years.

Earliest signs are muscle cramps, twitching, stiffness and wasting of one or more limbs.

The ‘split hand’ muscle involvement is specific for motor neurone disease [7, 8].

Memory, intelligence and personality are largely preserved.

More recently cognitive deficits have been described such as apathy, mood changes and disinhibition and a small minority progressing to FTD.

The patients with ALS maintain control of gaze and that of bladder and bowel functions.

There is no cure, and medical care is mainly palliation and involves a multidisciplinary approach which improves quality of life [6, 18, 19].

Riluzole, an inhibitor of glutamate release, has shown some promise in clinical trials [3].

Multiple Choice Questions

1. The following are true of amyotrophic lateral sclerosis (ALS) EXCEPT:
   A. About 5–10% of ALS patients are inherited as an autosomal dominant.
   B. As the disease progresses, muscle wasting becomes generalised with absent reflexes.
   C. Memory and intelligence
   D. The only drug approved by the FDA in the USA for ALS is riluzole.
2. The following are true in the diagnosis of motor neurone disease, EXCEPT:
   A. The tongue should be examined when within the mouth and relaxed.
   B. The electromyogram shows fasciculations, fibrillations and giant motor units with drop-out of motor unit potential units, but it is not useful.

C. Measurement of the motor conduction time from the cortex to muscle by magnetic stimulation may show slowing.
D. High-resolution MRI allows visualisation of the pyramidal tracts and atrophy or demyelination may be seen.

MCQ Answers

1 = B; 2 = B

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Multiple Sclerosis

39

Contents

Abstract

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease. The usual age of onset is between 20 and 40 years. Late-onset multiple sclerosis (LOMS) is defined as the first presentation of clinical symptoms occurring after the age of 50 years. The two groups 'adult-onset' multiple sclerosis (AOMS) and 'late-onset' multiple sclerosis (LOMS) defer in their demographic, clinical characteristics, disease course and response to treatment. Multiple sclerosis is extremely protean in its expression and severity. Based on the clinical course, MS has been categorized into (i) relapsing remitting MS (RRMS), (ii) secondary progressive MS (SPMS), (iii) primary progressive MS (PPMS) and (iv) progressive-relapsing (PRMS). About 80% of LOMS are affected by PPMS. About 94% of the patients with AOMS had RRMS. The diagnosis is based on careful clinical evaluation of the patient with investigations including MRI, CSF and evoked potentials. Treatment can be divided into treatment of the relapses, long-term immunomodulatory treatment and symptomatic relief. Patients often require care from a multidisciplinary team of healthcare providers.

Keywords

Multiple sclerosis · Adult-onset multiple sclerosis · Late-onset multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease [1] affecting the optic nerves, brain stem and spinal cord [2–4], and in all probability, it is an autoimmune disease [1, 5, 6]. The usual age of onset is between 20 and 40 years in about 70% of the patients [7]. It rarely occurs before 10 years but can occur as late as 67 years [7]. Onset of MS at the age of 81 years

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_36

has been reported in a recent cohort study [8]. It is significantly greater in women than in men [3]. The pathogenesis is unclear, a complex interplay among genetic susceptibility and environmental triggers [6, 7, 9], and sex hormones [10, 11] have been implicated leading to immune dysregulation. Current research supports an immunologic and viral pathogenesis [5]. Several observations such as high EBV antibody levels, universal EBV seropositivity and alterations in EBV-specific CD8(+) T-cell immunity among others implicate Epstein-Barr virus (EBV) in the pathogenesis [12].

Late-onset multiple sclerosis (LOMS) is defined as the first presentation of clinical symptoms occurring after the age of 50 years [13–15], and the prevalence ranges between 4% and 9.6% in different studies [13]. In a study of 640 MS patients, 30 (4.6%) was diagnosed as late-onset MS, ranging 50–62 years [14]. In another population study of 1417 MS, 3.4% had their first symptoms at 50 years or older [16]. The two groups 'adult-onset' and 'late-onset' differ in their demographic, clinical characteristic, disease course and response to treatment [15]. LOMS is three times more common in women than in men [17].

Clinical Manifestations

Multiple sclerosis is extremely protean in its expression and severity [9]. It usually starts with an acute neurological disturbance termed 'clinically isolated syndrome' (CIS) [2, 18] which is the first clinical demyelinating event affecting the optic nerves, the brain stem or the spinal cord [2, 4]. It is mandatory that CIS should unequivocally be seen in MS, such as unilaterally optic neuritis, bilateral internuclear ophthalmoplegia, incomplete transverse myelitis or cerebellar syndromes [19]. About two-thirds of the patients follow a relapsing-remitting course [2], and half of them develop secondary progressive MS with disability [4], progressive deterioration without relapses or remissions [1]. The remaining third have a benign course with minimal or no disability [4]. It is possible to predict the subsequent development of MS in patients with CIS with MRI scan, and about 80% with abnormal MRI convert to MS compared to 20% with normal MRI [2]. An CIS presentation with normal MRI scan has a low risk of converting to MS [20, 21]. In some patients, 15–20% will have a primary progressive course [18]. Disease-modifying treatments can delay the development of MS in selected CIS patients with abnormal MRI [2, 4].

Based on the clinical course, MS has been categorized into (i) relapsing-remitting MS (RRMS), (ii) secondary progressive MS (SPMS), (iii) primary progressive MS (PPMS) and (iv) progressive-relapsing MS (PRMS). Recurrent attacks or relapses occur with RRMS which vary in frequency and severity and a steady baseline between relapses [3]. SPMS commonly follows RRMS or may develop slowly after an initial CIS [3]. About 10% of patients with MS have PPMS and affects older individuals with spinal cord involvement characterized by progressive weakness with spasticity of the lower limbs. PRMS is an uncommon subtype with gradual progressive course punctuated by one or more relapses [3]. A follow-up of over 25 years demonstrated similarities in the progressive phases of PPMS and SPMS although the two groups differ with respect to sex ratio [10].

About 80% of LOMS are affected by PPMS [8, 22], but when the disease phenotype is set, the progression is similar to AOMS [22]. In their study, 94% of the patients with AOMS had RRMS. Both groups had typical multifocal supratentorial lesions without significant differences [8]. In the same study, spinal lesions were more common in LOMS, but cerebellar lesions were less frequent compared to patients to AOMS so was gadolinium-enhanced lesions [8]. Differences and similarities between late-onset multiple sclerosis (LOMS) and adult-onset (AOMS) multiple sclerosis are shown in Table 1.

Diagnosis

There is no single test including MRI that is diagnostic [23]. As the patients get older, there is a tendency to relate the symptoms to ageing, thus

Table 1 Differences and similarities between late-onset multiple sclerosis (LOMS) and adult-onset (AOMS) multiple sclerosis

	Late onset	Adult onset
Age of onset	>50 years	<50 years
Gender (F:M)	1.73:1	3:1
Prevalence	4–9.6%	
Clinical patterns		
RRMS	50%	94%
PPMS	80%	
SPMS	35%	
Symptoms		
Motor	54–90%	60%
Spinal	60–81%	48%
Sensory, ataxia cognition	No difference	No difference
Cerebellar	Less common	Common
Laboratory		
CSF-oligoclonal binding	76%	
VEPs abnormal	81%	
MRI	60–80%	98%
Progression	Faster	
Prescription-DMD		
IFN-beta (reduced disability)	Not significant	Significant
Rate of exposure	Low	

Information sources: Kis et al. [8], Pollack et al. [14], Martinelli et al. [13], Shirani et al. [15], Delalande et al. [16]

leading to delayed or misdiagnosis. The diagnosis is based on careful clinical evaluation of the patient with investigations including MRI, CSF and evoked potentials [18], and according to the revised McDonald criteria, the diagnosis is based on the clinical course and MRI findings [6]. The revised McDonald criteria incorporated defined MRI criteria to dissemination in space (DIS) and dissemination in time (DIT). DIS is shown by one or more MRI-detected lesions typical of MS, and DIT is shown by a current (active) and previous (non-active) lesion. The requirements have been simplified in the recent revised 2015 McDonald criteria allowing an earlier diagnosis from a single gadolinium-enhanced MRI which can provide evidence for dissemination in space and time [23] if there are both silent enhancing and non-enhancing lesions [24]. Pathologically the lesions in the MRI are non-specific, and characteristic lesions that support MS include ovoid lesions, Dawson fingers, corpus callosum lesions and asymptomatic spinal cord lesions [23]. Gadolinium also helps to rule out alternate diagnoses in the brain such as neoplasm, vascular malformations and leptomeningeal disease and in the case of the spinal cord spinal stenosis or tumour [23].

Treatment

The two clinical processes, relapses and progression, influence the course of MS [25]. Interferon-beta, glatiramer acetate and mitoxantrone are three therapeutic agents found effective in large three-phase studies [26]. Treatment can be divided into treatment of the relapses, long-term immunomodulatory treatment and symptomatic relief [6]. Corticosteroids are used for treatment of relapses [9], intravenous methyl prednisolone for 3 days [1, 18]. For RRMS patients, the first-line disease-modifying agents are interferon-beta and glatiramer [18]. Interferon-beta reduces the frequency of attacks and the progression of disability in RRMS [1]. In patients with SPPMS, PPMS and worsening RRMS, mitoxantrone, an immunosuppressant administered intravenously, reduces neurologic disability and relapse frequency [27] and reduces worsening of RRMS and SPMS [28]. Symptomatic treatment includes management of spasticity, pain, urinary problems, depression and anxiety, paraesthesia and fatigue [1, 18]. Patients often require care from a multidisciplinary team of healthcare providers, and primary care providers must have basic knowledge of the disease [5].

Impact

In the Western countries, the average age of people living with MS is about mid-50s [29]. The prevalence of MS is increasing more so in the very elderly because of the increase in life expectancy and the commencement of effective treatments. Individuals with MS have multiple chronic

conditions together with increased mental comorbidities [30]. The quality of life of the patients and that of the carers is reduced [31]. Depression and anxiety are vastly prevalent symptoms of MS. Lifetime prevalence rate of depression in MS is approximately 50%, and it is a major predictor of morbidity, mortality, quality of life and suicide risks among others [32], and life stress is positively correlated with current and future depressive symptoms [33]. A study on the psychological impact of MS that the patient experiences is related to enhanced appreciation of life and increase in spiritual pursuits and benefit-finding which was related to higher levels of anxiety and anger and not to depression [34]. MS is associated with a number of functional deficits and progressive disability, and loss of mobility is the most disabling aftermath [35]. Secondary progression occurs on average after 19 years after an exacerbating remitting onset of MS, and the median time to reach limitation of ambulation is 8 years, walking with stick 20 years and wheelchair bound 30 years [35]. The age at clinical onset of MS is significant; for the younger the onset, the younger the age at assignment of disability milestones, and females reached the disability milestones at an older age [36]. In the elderly, the symptoms of MS may be compounded by multiple problems such as comorbidities and multiple medications (Box 1).

Box 1 Key Points: Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease [1] affecting the optic nerves, brain stem and spinal cord [2–4], and in all probability, it is an autoimmune disease [1, 5, 6].

It rarely occurs before 10 years but can occur as late as 67 years [7].

Multiple sclerosis is extremely protean in its expression and severity [9]. It usually starts with an acute neurological disturbance termed 'clinically isolated syndrome' (CIS) [2, 18] which is the first clinical demyelinating event affecting the optic nerves, the brain stem or the spinal cord [2, 4].

About two-thirds of the patients follow a relapsing-remitting course [2], and half of them develop secondary progressive MS with disability [4], progressive deterioration without relapses or remissions [1]. The remaining third have a benign course with minimal or no disability [4].

The two clinical processes, relapses and progression, influence the course of MS [25].

Treatment can be divided into treatment of the relapses, long-term immunomodulatory treatment and symptomatic relief [6].

Multiple Choice Questions

1. The following are true of multiple sclerosis (MS), EXCEPT:
   A. Current research supports an immunologic and viral pathogenesis.
   B. Adult-onset MS is three times more common in women than in men.
   C. It usually starts with an acute neurological disturbance termed 'clinically isolated syndrome' (CIS).
   D. About one-third of the patients follow a relapsing-remitting course.
2. The following are true, EXCEPT:
   A. Gadolinium also helps to rule out alternate diagnoses in the brain such as neoplasm, vascular malformations and leptomeningeal disease.
   B. Pathologically the lesions in the MRI are non-specific.
   C. Lifetime prevalence rate of depression in MS is approximately 20%.
   D. Interferon-beta reduces the frequency of attacks and the progression of disability in RRMS.

MCQs Answers

1 = D; 2 = C

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Peripheral Neuropathy

40

Contents

Abstract

Peripheral neuropathy can be defined as a syndrome characterized by muscle weakness and wasting, altered or loss of sensation and vasomotor symptoms. It is less common in the old-old (>80 years) compared to the young-old (65–79 years), 25% vs. 46%. It may affect a single nerve or nerve root (axonopathy or radiculopathy). The nerve cell body may be the primary site of involvement (neuronopathy) and the sensory or autonomic ganglia (ganglioneuropathies). There are several causes. The clinical manifestations of neuropathy depend on the type, distribution and degree of damage of the nerve(s). Diabetes and alcoholism are the most common causes of polyneuropathy in Australia. Guillain-Barre syndrome (GBS) is the third most common. GBS has a bimodal age distribution, one peak in the young and another in the older population. GBS can be divided into demyelinating and axonal forms based on pathological and electrodiagnostic findings. They are the acute inflammatory demyelinating polyradiculopathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN), Miller Fisher syndrome and panautonomic neuropathy.

Keywords

Polyneuropathy · Guillain-Barre syndrome (GBS) · Acute inflammatory demyelinating polyradiculopathy (AIDP) · Acute motor axonal neuropathy (AMAN) · Acute motor sensory axonal neuropathy (AMSAN) · Miller Fisher syndrome · Panautonomic neuropathy

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_38

Introduction

Peripheral neuropathy may be acquired or hereditary, restricted to the peripheral nerve or part of a systemic illness. It is less common in the old-old (>80 years) compared to the young-old (65–79 years), 25% vs. 46% [1]. Diabetes and alcoholism are the most common causes of polyneuropathy in Australia. The average incidence of Guillain-Barre syndrome annually is 1–3 per 100,000 persons [2]. Idiopathic neuropathies are common in the old-old as compared to young-old (39% vs. 9%) [1].

Clinical Manifestations

The clinical manifestations of neuropathy depend on the type, distribution and degree of damage of the nerve(s). It may affect a single nerve or nerve root (axonopathy or radiculopathy). It may involve one or more nerves, and involvement of one is referred to as a mononeuropathy and more than one nerve as mononeuropathy multiplex, and vasculitis is the most common cause of acute multiple mononeuropathy [3, 4]. Plexopathy refers to involvement of the plexus, brachial or lumbosacral. The nerve cell body may be the primary site of involvement (neuronopathy), the sensory or autonomic ganglia (ganglioneuropathies) and peripheral nerves distally and more usually the lower extremities and later the upper (polyneuropathy). Sensory ganglionopathies are frequent [4] and manifest as unsteady gait and pseudoathetoid movements of the hand [5].

Weakness and muscle wasting occur when the motor axons are involved. The large sensory axons are responsible for proprioception, vibration sense and light touch. The small myelinated axons are composed of sensory axons and autonomic fibres and are responsible for pain and temperature. Autonomic dysfunction includes impotence, bladder dysfunction, postural hypotension, diarrhoea, constipation and loss of sweating. Pain in the form of burning dysthesia is seen with distal symmetrical neuropathies, for example, diabetes and alcoholism, and in mononeuropathies such as meralgia paraesthetica. Tendon reflexes are often diminished or lost.

Neurological abnormalities of B12 deficiency include a myelopathy with or without neuropathy [6]. The neurological symptoms include subacute combined degeneration, ataxia and mononeuropathies (optic neuropathy or olfactory atrophy and central visual scotomas) [7]. Other clinical manifestations include weakness, gait disturbance, incoordination and progressive cognitive decline [8]. The frequency of peripheral neuropathy as the sole manifestation is a subject of debate [9]. *Nutritional neuropathy* other than due to vitamin B_{12} deficiency can be due more importantly to vitamin B_1 (thiamine) and pyridoxine deficiencies. About 50% of the elderly have been found to be thiamine deficient. Thiamine deficiency in the elderly is associated with low intake and decreased activation of thiamine. The pathogenic role of alcohol in the development of neuropathy remains controversial. It usually presents as a sensorimotor polyneuropathy with numbness, weakness and sensory ataxia [10]. *Paraneoplastic neuropathies*. In a study of 520 patients with polyneuropathy, 2.3% were due to neoplasms [11]. Small cell lung cancer has long been known to develop neurological symptoms and signs. Paraneoplastic neurological symptoms also occur with other lung cancers, Hodgkin's disease, testicular and ovarian tumours, thymoma and breast cancer. *Sepsis and multiple organ failure* now called the systemic inflammatory response syndrome (SIRS) [12] are often accompanied by a form of sensorimotor axonal polyneuropathy referred to as critical illness neuropathy (CIN). The entire syndrome is characterized by septicaemia with encephalopathy, respiratory failure, respiratory dependency with weaning difficulty and sensorimotor neuropathy [13, 14]. CIN is often not recognized and frequently submerged in other manifestations of the syndrome [15]. There are difficulties in distinguishing CIN from critical illness myopathy (CIM). *Toxic neuropathies* occur following exposure to various drugs, heavy metals and industrial toxins. Sensory loss followed by motor weakness usually appears weeks after the exposure and evolves after the

chemical exposure has ceased, and recovery may take months or years [16].

Guillain-Barre Syndrome (GBS) or Acute Inflammatory Demyelinating Polyradiculopathy (AIDP)

GBS consists of different subtypes [17, 18] and can be divided into demyelinating and axonal forms based on pathological and electrodiagnostic findings [2]. They are the acute inflammatory demyelinating polyradiculopathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN), Miller Fisher syndrome and panautonomic neuropathy [19]. The Miller Fisher syndrome, Guillain-Barre syndrome with ophthalmoplegia, Bickerstaff's brain stem encephalitis and acute ophthalmoparesis without ataxia are closely related forming a continuous range and have been confirmed clinically [20]. It has been suggested that there is a bimodal incidence in adult life with peaks seen in late adolescence and in the elderly [21, 22].

Symptomatology

GBS causes limb weakness that progresses over a time period of days or at the most up to 4 weeks [23]. It generally presents as symmetrical motor paralysis with or without sensory and autonomic disturbances. Weakness with paraesthesias usually begins in the legs and progresses to involve the arms. The legs are more affected than the arms and more proximal than distal. Tendon reflexes are lost within a few days of onset. The progressive phase lasts from a few days to about 4 weeks of onset [24]. In about 98% of the patients, the weakness is maximum in 4 weeks [25]. The progressive phase is followed by a plateau phase of unchanging symptoms followed by improvement [19]. Pain is another common feature and is most severe in the shoulder girdle, back and posterior thighs [26]. About half the number with GBS have involvement of the facial and oropharyngeal muscles, and about one-third may require ventilatory assistance. Autonomic dysfunction includes cardiac arrhythmias and papillary muscle changes. Autonomic dysfunction and respiratory paralysis can be life-threatening. An unusual variant is the Miller Fisher syndrome with only ophthalmoparesis, ataxia and absent reflexes. The varied interaction between the T cells of different specificities and antibodies may be the reason for the different manifestations of GBS [27].

The presentation in the elderly is in no way different from that in the younger adults but there may be subtle variation which can overshadow the presentation in some [28]. This is often due to concomitant diseases and the frequent occurrence of coexisting neurological disease in the elderly and can delay or cause difficulty in diagnosis [28]. In the elderly, the presenting symptoms may be so mild and is often obscured by the multiple problems seen often in a frail elderly [28]. The Miller Fisher syndrome appears to be rare in old age [28]. Most patients improve over a period of months and about one-third may have residual weakness for some time (Box 1).

Box 1 Some characteristics of late-onset Guillain-Barre Syndrome

Incidence rate is higher.

Interval between onset and peak is shorter.

Antecedent illness is less frequent for example, gastro-intestinal symptoms.

Double vision and facial weakness less common.

CSF immunoglobin abnormality more marked.

Axonal variant more frequent.

Length of hospital stay longer.

Morality is higher.

Information sources: Alshekhlee [34], Sridharan et al. [35], Leung [36], Franca et al. [37]

Differential Diagnosis

GBS is frequently confused with other conditions which produce generalized weakness. In botulism, the hallmark of the disease is the descending paralysis. Ptosis and weakness of the extremities are frequent findings with weakness of the facial muscles, tongue, palate and larynx and extremities [29]. The disease progresses quickly over several days. Patients with GBS almost always have mild sensory abnormalities and increase in the cerebrospinal fluid protein concentration. The Miller Fisher syndrome is characterized by ataxia, areflexia ophthalmoplegia and mild limb weakness. The course in myasthenia gravis is more insidious, and the deep tendon reflexes and pupils are normal and the muscle weakness fluctuates. Patients with diphtheric paralysis have a history of severe pharyngitis [30] with subsequent weakness of the palate. Lyme disease usually begins with a unique skin lesion, erythema chronicum migrans followed by headache and meningeal irritation, and the tick is found, and in a small number of patients, neurological abnormalities may manifest after weeks or months [31]. Brain stem lesions are usually associated with corticospinal tract and cerebellar abnormalities.

Diagnosis

The diagnosis of GBS is based on the typical clinical features, examination of the cerebrospinal fluid and electrodiagnostic examination. The clinical features are characterized by progressive weakness of the legs and arms with diminished or absent reflexes. There is a high concentration of protein in the cerebrospinal fluid with few cells ('cytoalbuminologic dissociation) and in one study was seen in 25–75% of patients [20]. Early diagnosis of GBS is important, and electrodiagnostic studies characteristic of early GBS are an H response, abnormal F wave and abnormal upper extremity sensory nerve potential (SNAP) with a normal sural SNAP [32]. GM-1 Ab has limited value as a wide array of antigens have been described with antibodies to ganglioside. GM-1 has been recognized more frequently than others (up to 14–50%) [4]. Antibodies to ganglioside GQ1b have been found in the Miller Fisher variant [4]. Dense concentrations of GQ1b are found in the oculomotor nerves, and patients with oculopharyngeal palsy carry GQ1b/GT1a IgG [33] (Box 2).

Box 2 Key Points: Guillain-Barre Syndrome

GBS consists of different subtypes [17, 18] and can be divided into demyelinating and axonal forms based on pathological and electrodiagnostic findings [2].

It has been suggested that there is a bimodal incidence in adult life with peaks seen in late adolescence and in the elderly [21, 22].

In the elderly, the presenting symptoms may be so mild and is often obscured by multiple problems seen often in a frail elderly [8].

Ptosis and weakness of the extremities are frequent findings with weakness of the facial muscles, tongue, palate and larynx and extremities [9].

The diagnosis of GBS is based on the typical clinical features, examination of the cerebrospinal fluid and electrodiagnostic examination.

In the elderly, early recognition of GBS and intervention give the highest possible outcome of treatment.

Several randomized trials have shown that intravenous immunoglobulin and plasma exchange are equally effective but not corticosteroids [17, 18].

Treatment

Patients with GBS should be hospitalized for close observation for respiratory involvement, cranial nerve dysfunction and autonomic instability [19]. Autonomic nervous system may manifest as fluctuating blood pressure, cardiac dysrhythmias, gastrointestinal pseudo-obstruction and urinary retention. As respiratory muscles weaken, elective endotracheal intubation should be considered. Several randomized trials have shown

that intravenous immunoglobulin and plasma exchange are equally effective but not corticosteroids [17, 18]. Specific treatment should be instituted soon after diagnosis. High-dose IV immunoglobulin (IV ig, 400 mg/kg daily for 5 days) or plasmapheresis (five exchanges on 5–8 days) should be instituted [19, 23].

Chronic Inflammatory Demyelinating Polyradiculopathy (CIDP)

CIDP is considered a chronic variety of GBS. There is rapid onset of symptoms with relapsing or steady progressive course over a number of years. It is predominantly motor. The cerebrospinal fluid protein levels are normal at the onset of recurrence. The diagnosis is made on the basis of clinical symptoms and signs and electrodiagnostic examination and cerebrospinal fluid examination. In about a quarter of the cases, antibodies to the 28-kDa PO myelin glycoprotein had been identified [38]. Prognosis varies widely from near-complete recovery to relapses with partial recovery between relapses. Treatment includes the use of immunosuppressive drugs, plasmapheresis and IV immunoglobulin.

Evaluation

Evaluation of an individual with suspected neuropathy follows (I) a detailed history and general physical examination, (II) a meticulous neurological examination focusing on the diagnostic possibilities and (III) neurophysiological tests where appropriate. The history should include the presence of medical disorders, current and past medications, consumption of alcohol, possible exposure to toxic factors and sexual habits. The history should include the mode of onset, acute within days, subacute weeks to months and chronic insidious. Neurological examination should be focused on the pattern of nerve involvement, motor, sensory or mixed, whether it is a large fibre or small fibre neuropathy and evidence of autonomic involvement. Neurophysiological tests help to determine whether the neuropathy is predominantly axonal or demyelinating. Investigations that are done are shown in Box 3.

Box 3 Laboratory Investigations
Blood count, sedimentation rate
Blood sugar
Anti-GM, ganglioside IgM antibodies
CSF where indicated
Cutaneous nerve biopsy
Neurophysiological tests
Nerve conduction studies
Electromyography

The characteristic features of acute/subacute and chronic neuropathies are summarized in Tables 1 and 2.

Table 1 Characteristic features of acute/subacute neuropathies

Motor>sensory
GBS/AMAN: weakness prominent in the proximal muscle, legs > arms, tingling of extremities, triggering event usually an infection
Acute intermittent porhyria: motor weakness often preceded by abdominal pain, back and leg pain and parathesiae
Critical illness neuropathy: sepsis and multiple organ failure
Diphtheric: history of pharyngitis
Lyme disease: ascending paralysis
Toxins
Predominantly sensory
Paraneoplastic: small cell lung cancer, other cancers
Diabetes
Pyridoxine toxicity
Toxins
HIV
Mixed (sensory and motor)
AMSAN
Diabetes
Alcohol, nutritional: history of alcoholism
Toxins
Vasculitis

Information sources: Shields [3, 39], Hughes [7, 8], Steere et al. [31, 51], Nagaratnam et al. [14, 24], Glauser et al. and Chin [10, 16]

Table 2 Characteristic features of chronic neuropathies

Motor>sensory
CIDP: distal, proximal motor > sensory, relapsing and progressive
Toxins: heavy metals like lead; dapsone, cytosine, suramin
Predominantly sensory
Diabetes
Vitamin B_6 toxicity: pure sensory neuropathy
Paraneoplastic
Vitamin B_{12} deficiency: loss of position and vibration in extremities, may progress to involve the spinal cord
Hypothyroidism: paraesthesia of hands and feet, loss of ankle reflexes
HIV-1 distal painful sensory polyneuropathy. Develops during HIV infection
Mixed
Uraemia: symmetric distal sensorimotor neuropathy affecting the longest nerves in the extremities and dying back towards the spinal cord. The clinical symptoms – paradoxical heat sensation, impaired vibratory perception, etc. – indistinguishable from other metabolic axonopathies such as alcohol neuropathy, vitamin deficiencies, diabetes mellitus

Information sources: Shields [3, 39], Willison and Winer [40] and Pan [41]

Impact

Peripheral neuropathy is common in the elderly and causes impairment of proprioception, balance [42, 43], sensorimotor function, gait instability [44] and predispose to falls [43, 45]. The clinical signs include impaired position sense, inability to maintain unipedal stance for 10 s [42, 43] and decreased vibration sense and ankle reflexes [45]. Older adults are at greater risk of falling and fractures due to instability and weakness. Those prone to falls limit their activities [46], which lead to impairment of activities of daily living and quality of life. In older adults with diabetes, peripheral neuropathy is burdensome due to damaging effects on sensorimotor function, to gait instability and on activities of daily living [47–49]. There is a high prevalence of painful neuropathy among elderly diabetics and is significantly associated with falls [50]. In the elderly, painful sensory neuropathies are frequently experienced and may have significant impact on their quality of life and sleep [51]. Vitamin B_{12} has a great impact on neurological well-being [52], and the prevalence of vitamin B_{12} deficiency is high in the elderly and in nursing care facilities and may present with haematological and neuropsychiatric manifestations [53]. In the elderly older than 65 years, Guillain-Barre syndrome (GBS) is the third most common neuropathy [54] and associated with higher mortality among those older than 50 and increased further with increase in age [34].

Multiple Choice Questions

1. Which of the following is unlikely cause of dying back neuropathy?
   A. Diabetes mellitus
   B. Guillain-Barre
   C. Porphyria
   D. Alcoholism
2. Which is the most common cranial nerve involved in Guillain-Barre syndrome?
   A. III Nerve
   B. II Nerve
   C. VII Nerve
   D. V Nerve
3. The commonly identified pathogens in Guillain-Barre syndrome are, except:
   A. Epstein-Barr virus
   B. *Campylobacter jejuni*
   C. *E. coli*
   D. *Mycoplasma pneumoniae*

MCQ Answers

1 = B; 2= C; 3 = C

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Disorders of Neuromuscular Transmission

41

Contents

Abstract

Myasthenia gravis (MG) is an autoimmune disorder characterized by fluctuating muscle weakness and fatigue caused by antibodies directed against the nicotine acetylcholine (ACh) receptor (AChR) or against the muscle-specific tyrosine kinase (MuSK) receptor. The prevalence has increased over the past four to five decades, and the increase is mainly found in patients over the age of 50 years. Clinically and epidemiologically, it is possible to recognize two subtypes, the early-onset myasthenia gravis (EOMG) and the late-onset myasthenia gravis (LOMG). In MG, antibodies to the AChR cause a functional blockade of the binding site for ACh. Some MG patients do not have detectable AChR antibodies and are termed seronegative MG. In 2–3% of AChR-seronegative patients, there was seropositivity of anti-MuSK antibody. It had been reported that anti-AChR antibodies were seen in 65% with early-onset MG compared to 85% in the late-onset MG and elevated titers of anti-MuSK antibodies were similar. Ocular MG is more common in LOMG compared to EOMG so is myopathy. About 30% of late-onset MG patients without thymoma have antibodies to titin, whereas titin antibodies are uncommon in the early-onset MG. Significant therapeutic progress has been made in the treatment of MG and introduction of new modalities especially immunosuppressive, immunomodulating drugs, plasma exchange, and thymectomy. In Eaton-Lambert syndrome (E-LS), there is a reduction in the release of acetylcholine from the motor nerve terminals. There are substantial differences between E-LS and MG

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_39

in the pathophysiology, clinical features, electromyographic changes, and treatment. More than half the patients with E-LS are associated with malignancies such as small cell lung cancer (SCLC) non-small cell lung cancer, and lymphoma, among others. The antibodies in E-LS prevent the opening of the calcium channels, and hence the release of ACh and voltage-gated calcium channels (VGCC) antibodies has been reported in 75–100% of patients with L-ES. Guanidine increases the release of ACh.

Keywords

Myasthenia gravis · Late-onset myasthenia gravis · Early-onset myasthenia gravis · Muscle- specific tyrosine kinase (MuSK) receptor · Eaton-Lambert syndrome

Introduction

About one-third of all cases occur in the older population [1], and over the last 40 years, the occurrence after the age of 50 years is common [2]. In the early onset, most patients are between the ages of 15 and 40 years and most are females, and in the late onset, they are between ages 60 and 70 years and the males predominate [3–5]. In general, women are affected twice as often as men, and men formed two groups, one group with peak of onset between 25 and 30 years and the other between 60 and 70 years [6] (Fig. 1). Fig 1. shows the physiology of normal neuromuscular transmission.

Clinical Symptomatology

Clinically and epidemiologically, it is possible to recognize two subtypes, the early-onset myasthenia gravis (EOMG) and the late-onset myasthenia gravis (LOMG). The patients with MG often have muscle weakness and fatigability worsening later in the day. It worsens with exertion and improves with rest. Weakness of the eye muscles is usually the first complaint. Ocular MG presents as ptosis, diplopia, and visual impairment. Ocular MG is more common in LOMG compared to EOMG [7]. Almost all the patients with MG have ptosis or diplopia at some time of their illness. About 80% of the patients with ocular MG will develop other symptoms, and the remaining 20%, the disease may be confined to the eye muscles.

In the bulbar type, the muscles of swallowing, chewing, and speech may be affected in the first instance. In generalized MG, the eyes as well as other parts of the body are involved. There is weakness of the neck muscles, and the head suddenly drops forward. There is weakness of the limbs more proximally and may involve the respiratory muscles. Respiratory muscle and limb weakness are rare at the onset of the disease [8]. Myopathy is more common in the LOMG [9], and facial and tongue muscle wasting occur early in MuSK-MG [10]. Bulbar symptoms are more marked with MuSK-MG compared to AChR-MG, whereas ptosis and external ocular muscle weakness are more prominent with AChR-MG [10]. MuSK antibody positive seronegative shows a marked female preponderance [12]. MuSK-MG has been clinically recognized to be of three types [12], namely, (i) generalized weakness; (ii) focal forms involving the neck, shoulder, and respiratory muscles; and (iii) severe form of bulbar weakness frequently present in respiratory crisis [11, 13, 14] (Box 1). Table 1 shows some of the differences between early onset MG and late onset MG.

Box 1 Clinical manifestations

Ocular ptosis, diplopia, visual impairment
Bulbar involvement of muscles of swallowing and speech
Generalized eye and other parts of the body – neck muscles, proximal limb weakness, respiratory muscles

Progression to severe disease may be more common in MG with onset after the age of 50 years. There is a somewhat increased incidence of weakness of the bulbar muscles [28], and this has been attributed to the increased incidence of thymoma [29]. About 40% of all thymoma cases are associated with MG [22]. The course of the disease is more severe, and crisis occurs more often than in

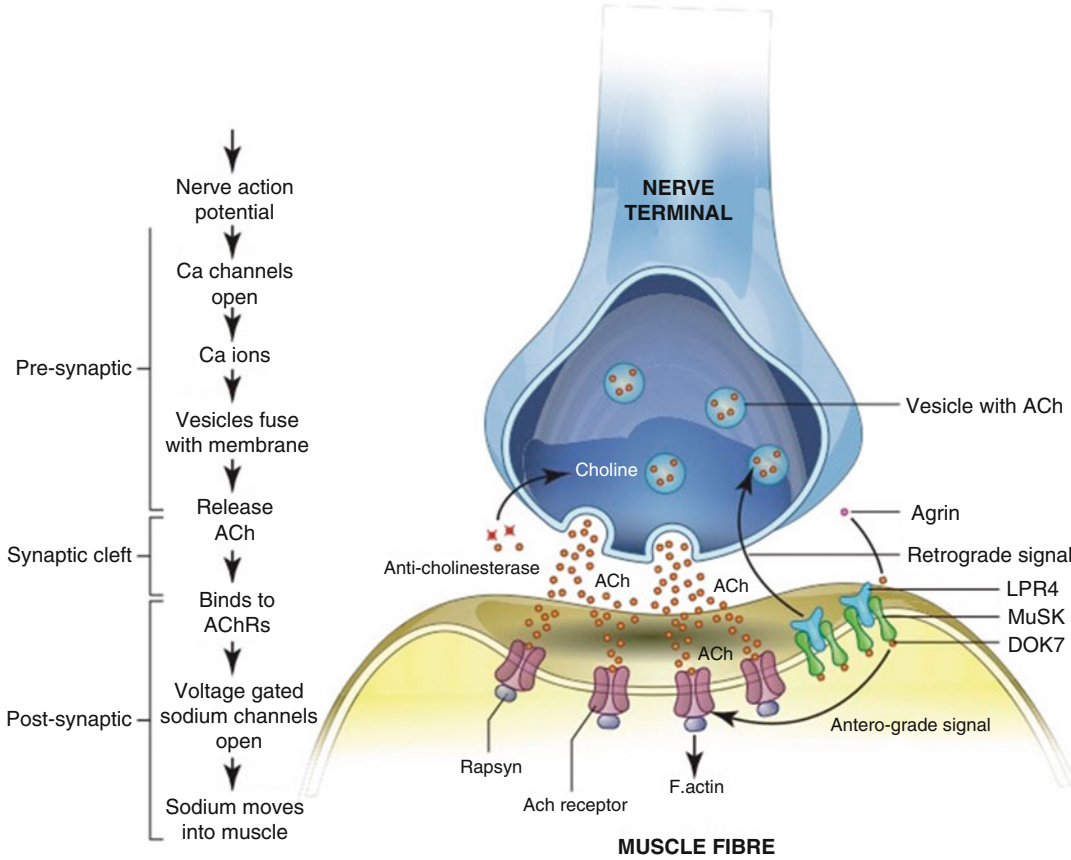

Fig. 1 Neuromuscular junction (Reproduced from Nagaratnam N, Nagaratnam K, Cheuk G: Diseases of the Elderly, Age Related Changes and Pathophysiology. Springer, 2016)

those without thymoma. Thymoma is more common in the late-onset MG, and the response to thymectomy is more uncertain in them than in younger patients [22, 29, 30]. In the late onset, antibodies to AChR are less often found than antibodies to other muscle components [22, 29, 30]. About 30% of late-onset MG patients without thymoma have antibodies to titin, whereas titin antibodies are uncommon in the early-onset MG [22]. Myasthenic crisis is more common in LOMG [7], and MuSK-MG is a high risk for recurrent crises [10].

Diagnosis

The diagnosis is based on the clinical presentation, neurological examination, electrophysiological testing, and immunological studies. Diagnosis in elderly may be difficult because of the age-related changes, for instance, there is decrease in the total eye area with sagging and ptosis may be difficult to recognize [4]. The Tensilon (edrophonium test) is a clinical test to look for improvement in any weak area after its administration. The other is the ice test, where an ice pack is placed over the eye for a minute or two and to examine for any improvement in the eyelid drooping. The standard blood test is the detection of antibodies against acetylcholine receptor (AChR), and the finding of anti-AChR antibody is highly specific for MG (>99.9%) [19]. The positivity was proportional to the clinical severity of MG (ocular MG: EOMG 71%, LOMG 88%; severe generalized MG: EOMG 89%, LOMG 98%) [19]. AChR antibodies are only detectable in about half the patients with

Table 1 Some differences between early-onset and late-onset myasthenia gravis

	Early-onset myasthenia gravis (EOMG)	Late-onset myasthenia gravis (LOMG)
Age of onset	<49 years	>50 years
Gender	F>M	F=M
Prevalence and incidence	Unchanged	Increased in middle and old
Etiology		
Genetic	HLA-A1D8-DRL haplotype	HLA-B7-DR2 haplotype
	DR3 positive	Less common
Clinical characteristics		
Extraocular symptoms		Appear more quickly
Dysphagia, axial, and proximal limbs weakness		
Ocular symptoms		More common
Course of disease		More severe
Myopathy	Less common	Common
Disease severity	Less severe	More severe
Myasthenic crisis	Common (13%)	Equally common (13%)
Pathophysiology		
Thymoma		More common
Hyperplastic	Common	
Hyperplastic + thymoma		Common
Immunopathology		
Antibodies against	Ocular MG 71%	Ocular MG 88%
AChR	Severe generalized MG 89%	Severe generalized MG 98%
Non-AChR muscle antibodies		More frequent
Anti-titin antibodies	Rarely found	Found in 50% of LOMG
Treatment		
Acetylcholinesterase inhibitor		Effect temporary
Thymectomy	Better	Poorer
Long-term steroid complications		Common
Immunosuppresive drugs		Unpredictable

Reference numbers: Zivkovic et al. [7], Somnier and Trojaburg [9], Suzuki et al. [15], Romi [16], Gunji et al. [17], Wang et al. [18], Somnier [19], Schon et al. [20], Maniol et al. [21], Aarli [22], Barbaud et al. [23], Meriggioli and Sanders [24], Howard [25], Keesey[26], and Chaudhry et al. [27]

ocular myasthenia compared to 80–90% with generalized form of MG [8]. In the elderly, the mean concentration of AChR antibodies is lower than in the early-onset or thymoma-associated MG [4]. About 30% of late-onset, non-thymoma MG patients have antibodies to titin which seems to be associated with higher frequency of DR7 antigen and decrease of DR3 antigen [4]. Anti-titin antibodies can be considered to be a marker for LOMG [31]. In a patient without AChR antibodies, the diagnosis is difficult. A normal or negative result does not exclude the diagnosis. Slight increases may be found in other conditions such as rheumatoid arthritis, D-penicillamine, lupus erythematosus, and thymoma without myasthenia gravis. In the others where there are no autoantibodies (seronegative), the history, clinical examination findings, reaction to anticholinesterases, and electromyographic studies may strongly point to the diagnosis. More than half the patients have been shown to have antibodies against muscle-specific kinase (MuSK) present in the neuromuscular junction [32].

One of the nerve tests specific for myasthenia gravis is decrement of the compound muscle action potential (CMAP) in the repetitive stimulation test [32]. The other is the single-fiber EMG which is the most sensitive nerve test of neuromuscular transmission and shows jitter in some

Table 2 Comparison of the different tests in MG

Test	Comment
1. Tensilon test	Only in clear-cut cases, may be equivocal in ocular and can give false-positive results
2. Ice test	As above, the test cannot be done if there are no weak muscles
3. Serum antibodies to AChR	Detectable only in 50% ocular disease and 80% in generalized. Occasionally elevated in other conditions. Normal or negative result does not exclude MG
4. Decrement in repetitive stimulation test	Frequently normal in the mild cases as well as in pure ocular disease
5. Single-fiber EMG	Most sensitive test for MG but is present in other conditions

Information sources: Somnier [19] and Diagnosis [32]

muscles in almost all patients with myasthenia gravis [32]. Table 2 compares the different tests and their limitations.

Other myasthenic syndromes especially Eaton-Lambert syndrome should be considered in the seronegative patients with fluctuating weakness. MG mimics many neuromuscular diseases and even illnesses such as depression and chronic fatigue syndrome, and drug-induced myasthenia must be excluded for all patients [33]. In patients with bulbar symptoms, the differential diagnosis should include neuromuscular diseases such as amyotrophic lateral sclerosis, ocular pharyngeal atrophy, or myotonia dystrophica.

Treatment

Significant therapeutic progress has been made in the treatment of MG and introduction of new modalities especially immunosuppressive, immunomodulating drugs, plasma exchange, and thymectomy (Box 2). Based on the age of onset, distribution of weakness, presence or absence of antibodies, and histology of the thymus several subtypes have been recognized which require different treatment strategies [24, 33]. The morbidity and mortality of this disease have decreased. Treatment with anticholinesterases and corticosteroids is sufficient for ocular MG; however, other immunosuppressive therapy may also be needed. Serious side effects are seen in LOMG with corticosteroid treatment and appear to depend on the dosage, duration of treatment, and patient characteristics [34]. Pyridostigmine is usually the first line of treatment followed by corticosteroids and azathioprine if the response is insufficient. In generalized MG, a wide array of immunosuppressive treatments are available. Immunosuppression has benefited in all clinical forms of MG, rate of remission ranging from 85% in ocular myasthenia to 47% in thymoma-associated disease, and the highest side effects were seen in LOMG and the lowest in EOMG [35]. With azathioprine, the effect may be delayed by 4–8 weeks although it reverses symptoms, whereas with cyclosporine, most patients improve in 12 months, and this is maintained as long as therapeutic doses are given [25]. With cyclophosphamide, more than 50% of the patients become asymptomatic after 1 year [25]. In patients intolerant to azathioprine, mycophenolate mofetil is an option [35, 36]. For severe or resistant cases, co-treatment with intravenous immunoglobulin and plasma exchange may be considered in the short term [33]. Malignant thymoma may be present in about 15% MG patients and may require thymectomy. For non-thymoma patients with generalized MG, complete transsternal thymectomy is recommended. Though it seems promising, the use of biological drugs such as CD20 antibodies is limited [33] (Table 3 and Box 3).

Box 2 Current Therapies For Myasthenia Gravis

Anticholinesterase therapy
- Immunosuppressant therapy
- Plasmapheresis (plasma exchange)
- Intravenous immunoglobulin
- Thymectomy
- Other therapies, atropine, Pro-Banthine, ephedrine

Table 3 Therapies in myasthenia gravis

Therapy	Indication	Dosage	Limitations	Adverse effects	Maximal effect
I. Anticholinesterases					
Pyridostigmine	First line in most MG patients	60 mg tid to 120mgq3h	Suffice for ptosis not for diplopia or generalized MG	GI effects – salivation, abdominal pain, diarrhea, nausea Precautions in bronchial asthma overdose – cholinergic crisis	Not enough for generalized MG
Neostigmine for IV use in intensive care units					
II. Immunosuppressive					
Prednisone	Refractory, ocular, generalized MG	1 mg/kg/ body weight daily	Long-term effects	Gastric ulcer, osteoporosis	Improve symptoms within weeks
Azathioprine	Immunosuppression-steroid sparing	2.5–3.0 mg/ kgqd 1.5–2.5 mg/ kgqd maintenance	Long-term risk of skin cancer	Rash, hepatitis, myelosuppression, hair loss, nausea	Response slow 6–12 months
Cyclosporine	Steroid sparing	3–4 mg/kg	Assess for renal toxicity	Hypertension, nausea, increased body hair	Within weeks maximum in 7 months
Cyclophosphamide	Refractory steroid sparing	3.5 mg/kg daily	Expensive	Anorexia, nausea, hair loss	2 weeks to 2 months
Mycophenolate	Alternative to azathioprine	1 g bd	Expensive	Few, nausea, diarrhea	
III. Immunomodulating					
Plasma exchange	Acutely ill MG, for crisis management	15 exchanges, 10 days	Over-expensive	Complicates more frequent in the elderly	
Immunoglobulin	Acutely ill MG	2 mg/kg (2–5 days)	Cost	Myalgia, chills, fever, headache, chest discomfort	Benefits not well demonstrated
IV. Thymectomy					
Thymoma	Moderate generalized MG	Major surgery	Benefits poorly documented	No known long-term effects	7–10 years after surgery to reach peak

Information sources: Howard [25], Keesey [26], Chaudhry et al. [27], Kaminski et al. [37], and Ciafaloni et al. [38]

Box 3 Key Points: Myasthenia Gravis

- In MG, antibodies to the AChR cause a functional blockade of the binding site for Ach [33].
- The autoantibodies are directed either against the muscle nicotine Ach receptor or the muscle-specific tyrosine (MuSK) [33].

Box 3 Key Points: Myasthenia Gravis (continued)

- Titin and ryanodine receptor antibodies are seen in 95% of thymic MG and in 50% of late-onset MG.
- Antibodies against LRP4 were found in patients directed against AChR or MuSK [16, 39].

(*continued*)

Box 3 Key Points: Myasthenia Gravis
(continued)

- Clinically and epidemiologically, it is possible to recognize two subtypes, the early-onset myasthenia gravis (EOMG) and the late-onset myasthenia gravis (LOMG).
- MuSK-MG has been clinically recognized to be of three types [12].
- Thymoma is more common in the late-onset MG, and the response to thymectomy is more uncertain in them than in younger patients [22, 29, 30].
- Myasthenic crisis is more common in LOMG [7], and MuSK-MG is a high risk for recurrent crises [10].
- In generalized MG, a wide array of immunosuppressive treatments are available.
- The mortality and morbidity of MG have decreased dramatically with the rate 3–4% [40].

Eaton-Lambert Syndrome

Introduction

Eaton-Lambert syndrome (E-LS) is an autoimmune disorder of neuromuscular transmission characterized by a reduction in the release of acetylcholine from the motor nerve terminals. Autoantibodies against voltage-gated calcium channels (VGCC) are detected in 85% of the patients [41]. VGCC antibodies are generally associated with paraneoplastic as well as non-paraneoplastic cerebellar degeneration [42, 43]. More than half the patients with E-LS are associated with malignancies such as small cell cancer (SCLC) [41–44] and non-small cell lung cancer [45], lymphoma, T-cell leukemia, and transitional cell carcinoma of the bladder. Three times as many men than women are affected, and the mean age is 62 years [43]. It resembles myasthenia gravis (MG), but there are substantial differences in the pathophysiology, clinical features, electromyographic changes, and treatment.

Clinical Manifestations

E-LS can exist in two forms, paraneoplastic (P-LEMS) and non-paraneoplastic (NP-LEMS) [46]. The clinical triad is proximal weakness, absence of weakness, and autonomic dysfunction [42, 44]. Symptoms of E-LS begin with weakness of the pelvic muscles and thigh with tenderness and weakness of both arms [47, 48]. Due to involvement of the pelvic girdle muscles, the patient walks with a waddle. At the beginning, exercise improves the weakness, but weakness may become more pronounced as exercise continues. There may be bilateral ptosis. Autonomic dysfunction are the second typical symptoms in E-LS such as dryness of the eye and skin followed by difficulty in talking and swallowing, sweating abnormalities, postural hypotension and erectile problems in men, and constipation [49]. Some patients present with cerebellar ataxia (paraneoplastic cerebellar degeneration, PCD) [42] often accompanied.by SLCC and high titers of VGCC antibodies [44] in about 40% of patients [42]. About 20–40% of these patients have clinical and electrophysiological features of E-LS [42].

Diagnosis

The diagnosis is based on the clinical manifestations and characteristic electromyographic patterns. Electrophysiological examinations show reduced amplitude compound muscle action potentials that increase with repetitive nerve stimulation by over 100% [41, 43 44]. Voltage-gated calcium channels (VGCC) antibodies have been reported in 75–100% of patients with E-LS in those who have small cell lung cancer and 50–90% without underlying cancer [50]. Assay of VGCC antibody titers and electrophysiological

tests will help to distinguish E-LS from other disease of neuromuscular function. Patients with E-LS should be thoroughly screened for a previously undetected cancer.

Treatment

First step is the treatment of the malignancy, if this had been identified. In patients who have a cancer, effective treatment of the cancer frequently produces improvement of the weakness as well [51]. Cholinesterase inhibitors which are effective in the treatment of MG do not produce significant improvement in patients with E-LS. The use of agents that improve neuromuscular transmission by increasing release of ACh will improve the weakness [51]. Guanidine increases the release of ACh. 3, 4-diamino pyridine has been shown to improve symptoms by increasing the release of ACh and has shown to increase muscle strength [46, 52, 53]. Prednisone, plasma exchange, azathiopurine, and intravenous gamma globulin are effective treatments [50] and in patients unresponsive to 3,4-diaminopyridine [42]. Prednisolone and/or in combination with immunosuppressants may achieve long-term control [43, 44]. Intravenous gamma globulin and plasmapheresis have short effect [43, 44].

Impact

The mortality and morbidity of MG have decreased dramatically, and this is largely due to new treatment strategies [54]. The principal risk factors are age older than 40 years, short history of severe disease, and thymoma [40]. Fatigue is a common symptom of MG, and it has been reported that it produces mild to moderate effects on cognitive, social, and physical function [55]. Some patients with LOMG do not improve after thymectomy, and older patients are more prone to complications of long-term steroid therapy [56].

Multiple Choice Questions

1. The following are true regarding neuromuscular transmission, except:
   A. Acetylcholine and Na(+) channels are concentrated in neuromuscular junction postsynaptic folds, and both are depleted in myasthenia gravis.
   B. In Eaton-Lambert syndrome the autoantibodies are directed against the calcium-gated channels.
   C. Botulinum toxin enhances the release of acetyl choline from the presynaptic channels.
   D. In acquired neuromyotonia, the antibodies are directed against the potassium-gated channels.
2. The following symptoms are suggestive of myasthenia gravis, except:
   A. Diplopia and ptosis
   B. Wasting of muscles
   C. Difficulty in swallowing
   D. Head suddenly falling forward
3. Which is the most sensitive test for the diagnosis of myasthenia gravis?
   A. Single-fiber EMG
   B. Determining the acetylcholine receptor antibodies
   C. Tensilon test
   D. Decrement in repetitive stimulation test

MCQ Answers

1 = C; 2 = B; 3 = A

Extending Matching Questions

A. Ocular myopathy
B. Myasthenia gravis
C. Horner's syndrome
D. Myotonia atrophica
E. Third nerve
F. Cortical ptosis

Patients have one or more of the following: weakness of external ocular muscles (EOM), internal ocular muscles, ptosis, and gaze palsy.

Choose the most likely diagnosis from the list above. Each option can be used only once.

1. A 62-year-old man suddenly developed weakness of his left side. On the third day, he had

bilateral ptosis (OD>OS), with gaze deviation to the left. He had contraction of his frontalis muscles.

2. A 60-year-old woman had difficulty in keeping her head up. She was not on any medication. She had bilateral ptosis with weakness of the superior oblique and lateral rectus in her left eye. The pupils were normal.
3. A 64-year-old man had digital ischemia of his right hand. He had cervical sympathectomy following which he developed partial ptosis of his right eye and small pupil.
4. A 64-year-old woman was seen with bilateral ptosis from early childhood. External ocular movements were normal and so were her pupils. There was a family history.

EMQ Answers

1 = F; 2 = B; 3 = C; 4 = A

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Epilepsy

42

Contents

Abstract

Epilepsy often develops for the first time in old age. The active epilepsy prevalence rate is approaching 1.5% amongst the 65 years and older which is about twice the rate of younger people. Aetiology of seizures varies amongst the different age groups. In the elderly, cerebrovascular and neurodegenerative diseases are the leading causes of epilepsy. In the elderly, stroke is the common cause of seizures. Status epilepticus occurs in 12% of stroke patients and remains a life-threatening event. Periodic lateralising epileptiform discharges (PLEDs) have been commonly associated with cerebral infarction but also with other cerebral diseases such as encephalitis, tumour and demyelinating diseases. Manifestations depend on the type of seizure which may be classified as partial (focal) or generalised. Elderly individuals who have seizures must be carefully evaluated. Investigations should include neuroimaging. A common manifestation of epilepsy in the elderly is non-convulsive status epilepticus (NCSE). Most elderly people respond well to antiepileptic drugs (AEDs) including low doses of AED and are more likely to remain seizure-free than the younger patients. Monotherapy is the main goal of epileptic treatment, and majority can be controlled on a single agent. The doses that seem to be more appropriate are in the lower levels than the therapeutic ones, and the clinician is best placed to decide. Patients with epilepsy have neuropsychological impairments including emotional distress, behavioural disorders and social isolation and the quality of life.

Keywords

Epilepsy · Seizures · Status epilepticus · Periodic lateralising epileptiform discharges (PLEDs) · Non-convulsive status epilepticus (NCSE)

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_40

Introduction

According to the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) 'an epileptic seizure is a transient occurrence of signs and symptoms due to excessive or synchronous neuronal activity in the brain' [1]. It is characterised by a predisposition to generate epileptic seizures and neurobiologic, cognitive psychological and social consequences of the condition [1]. The former is an event, whereas the latter is a disease [2]. Epilepsy often develops for the first time in old age. The incidence of a first seizure is 52–59 per 100,000 in persons 40–59 years of age but rises to 127 per 100,000 in the 60 years and over [3]. The active epilepsy prevalence rate is approaching 1.5% amongst the 65 years and older which is about twice the rate of younger people [4]. Seizures in the elderly occur equally in both sexes. Focal seizures occur at any age but most commonly occur after the age of 65 years [5].

In the elderly, cerebrovascular and neurodegenerative diseases are the leading causes of epilepsy. Furthermore seizures are the most common neurological consequence of stroke. Approximately 10% of stroke patients experience seizures [6]. The average age of post-stroke seizures (PSS) is 55.4 years [7]. Late-onset seizures have a peak onset within 6–12 months after the stroke [8]. In subarachnoid haemorrhage it is 8.5%, and the late onset occurs three times more often than the early onset [9]. Epilepsy (recurrent seizures) develops in 3–4% of stroke patients and accounts for 30–40% of cases of epilepsy [10]. In a population-based study of the incidence of epilepsy and unprovoked seizures for persons with identified aetiology, cerebrovascular disease accounted for 35% in the age group 35–65 and 67% in the elderly aged more than 65 years [1].

Seizures can be caused by a wide range of underlying conditions including focal brain lesions (head trauma, stroke, tumour), infections of the CNS (brain abscess, meningitis, encephalitis), metabolic disorders, (hyperglycaemia, hypoglycaemia, hypernatraemia, hyponatraemia, hypocalcaemia, hepatic failure, uraemia), drugs/toxins (alcohol, antipsychotics, antidepressants), neurodegenerative disorders (Alzheimer's disease) and other disorders such as hyperpyrexia, cerebral hypoxia and cerebral oedema. Aetiology of seizures varies amongst the different age groups. Compared with the younger people, the elderly are more prone to develop seizures whether provoked by acute illness ('provoked' or 'acute symptomatic seizures') or without ('unprovoked' seizures) immediate cause [12]. A cause can be identified in more than 60% of elderly people and is classified as remote symptomatic epilepsy [13].

Seizures are the result of focal or generalised disturbance of cerebral function which may be due to various cerebral or systemic disorders. Seizures after stroke occur in two phases, one, immediately after the stroke and is short lived, and the other during the first year after stroke and tends to be repetitive. Post-stroke seizures account for 30–40% of cases of epilepsy [10]. Large cortical lesions, decreased consciousness and haemodynamic and metabolic (mainly renal) disturbances are associated with early-onset seizures in ischaemic strokes [9], whereas in haemorrhagic stroke the products of blood metabolism such as haemosiderin may cause a focal cerebral irritation leading to seizures [9]. Lobar haematomas are frequently accompanied by early-onset stroke-related seizures [6]. Seizures are more commonly associated with haemorrhagic rather than with ischaemic stroke [14]. The late onset is considered to be unprovoked seizures that occur from partially injured brain giving rise to an epileptic focus [15].

Status epilepticus occurs in 12% of stroke patients [9] and remains a life-threatening event. In a large series of patients with post-stroke seizures, 9% had status epilepticus [16]. Periodic lateralising epileptiform discharges (PLEDs) have been commonly associated with cerebral infarction but also with other cerebral diseases such as encephalitis, tumour and demyelinating diseases [17]. PLEDs are characterised by repetitive spike or 'sharp' wave discharges and focal or late changes over one hemisphere and occurring at fixed time intervals [17]. Patients with acute stroke and PLEDs are predisposed to the

development of seizures [18]. PLEDs are observed in 25% of patients with early-onset seizures and only 1% in the late onset [6]. About 26.5% of stroke patients with late-onset seizures have a combined frequency of PLEDs, intermittent rhythmic delta activity (IRDAs) and diffuse slowing on EEG compared with 6.2% in those without seizures [9]. The relationship between PLEDs, acute stroke and subsequent development of epilepsy is not clear. PLEDs have been considered as a part of status epilepticus [19]. In reperfusion syndrome or hyperperfusion syndrome, there is disruption of the blood-brain barrier, cortical irritability and epileptic seizures and presents as ipsilateral headache, contralateral neurological deficits and seizure which may be focal or generalised [20].

Clinical Manifestations

Manifestations depend on the type of seizure which may be classified as partial (focal) or generalised. In the former, the excess neuronal disturbance is contained within one region of the cerebral cortex. In generalised seizures, the disturbances bilaterally and diffusely involve the cerebral cortex. Up to 70% of seizures in the elderly are of the focal onset with or without secondary generalisation [11, 21]. Focal seizures depend on the site of the dysfunction, and focal manifestations could be chewing movements or smacking of the lips (anterior temporal lobe), visual hallucinations (occipital lobe), olfactory hallucinations (antero-medial frontal lobe) and localised numbness or tingling (parietal lobe-sensory). Complex partial (focal) seizures usually present with atypical features such as episodes of confusion, periods of inattention, memory **lapses** or apparent syncope [18].

Evaluation of an Elderly with Seizures

Elderly individuals who have seizures must be carefully evaluated. Evaluation includes a thorough history and more importantly from a witness as to the event followed by meticulous neurological examination to look for signs of focal neurological disease. A general examination to exclude other conditions which may mimic seizures must be performed. Investigations should include neuroimaging. MRI is more sensitive than CT scan to pick up more subtle abnormalities. Limitations of the EEG should be recognised. A normal EEG does not rule out epilepsy. The diagnosis of epilepsy is usually clinical by nature of the attacks supported by EEG evidence. The EEG findings however must be convincing in cases where clinical information is wanting. Changes in mental status in the elderly can be due to a number of causes, and when an elderly patient presents with change in mental status, the diagnosis of epilepsy can be difficult. A common manifestation of epilepsy in the elderly is non-convulsive status epilepticus (NCSE). The patient presents with confusion or disturbed sensorium [22]. Many of them do not have a history of epilepsy [23], and there is often a long delay in the diagnosis [24]. Elderly patients with unexplained episodes of confusion, disorientation, decreased consciousness and motor or sensory symptoms should be evaluated for seizures, and an EEG-video monitoring should be considered for such evaluation [22].

The differential diagnosis includes other causes of seizures and the conditions that can mimic seizures. The clinical presentation may not be typical; atypical seizure forms are seen especially in older people. They may present with symptoms of acute confusional state, behavioural changes or syncope [25]. Changes in the mental status in the elderly can be due to a number of causes, and when the elderly patient presents with change in the mental state, the diagnosis of epilepsy can be difficult. A common manifestation in the elderly is non-convulsing status epilepticus (NCSE). NCSE is now being increasingly recognised with the use of evolving EEG technology [26]. NCSE can occur in various settings, in patients with epilepsy or arising de novo or in the setting of acute or remote symptomatic conditions [26]. Many may not have a history of epilepsy [23]. There should be increased awareness and increased diagnostic

suspicion. Elderly patients with unexplained episodes of confusion, disorientation, decreased consciousness and motor and sensory symptoms should be evaluated for seizures, and an EEG-video monitoring should be considered for such evaluation [21].

There are a number of conditions that can mimic seizures especially in the elderly. Transient ischaemic attacks (TIA) can be confused with seizures. Inhibiting seizures simulating TIA is seen in 7.1% of cases [9]. The 'shaking limb' TIAs which occur with carotid artery stenosis can be distinguished by its postural character, occurring on standing and not involving the facial muscles and cognition [27]. Others in the differential diagnosis include syncope, migraine, toxic metabolic diseases and narcolepsy.

Treatment

The so-called therapeutic levels can cause problems especially for the elderly for these levels have been derived from a non-elderly population [28]. The doses that seem to be more appropriate are in the lower levels than the 'therapeutic' ones, and the clinician is best placed to decide [28]. The elderly are very susceptible to adverse effects, and clear-cut consideration should be given to the most appropriate antiepileptic drug minimising its side effects and potential drug interactions. To avoid toxicity, it is generally recommended that the starting dose is low and titrating slowly upwards. Most elderly people respond well to antiepileptic drugs (AEDs) including low doses of AED [29] and are more likely to remain seizure-free than the younger patients [30].

With increasing age, the pharmacokinetics and pharmacodynamics of epileptic drugs undergo alteration [31] in receptor affinity and lead to altered drug sensitivity. In the elderly, the clearance of most old and new AEDs is reduced by 20–40% compared to the younger patients [30]. Thus, the mechanisms of the actions of the drugs should be taken into account as well as metabolic routes to minimise drug interactions. In the elderly, the biological age is more important than the chronological age in terms of choice and usage of AEDs [12]. AEDs that cause cognitive impairment are best avoided. In selecting a drug for the elderly, special consideration must be given to concomitant medical conditions [28]. For patients with hepatic failure, the first consideration in the choice of the drug should be an agent mainly excreted by the kidney and for one with renal failure an agent that is metabolised by the liver.

Generally there are no significant differences in the effectiveness of the AEDs if they are adequately used in relation to the type of seizure and a distinction of generalised seizures from focal and secondary generalised seizures [5]. The newer drugs, gabapentin, lamotrigine, oxcarbazepine, levetiracetam, tiagabine and topiramate, appear to be better tolerated but are more expensive. They have however basically not changed the principles of epilepsy treatment [5]. The older drugs phenytoin, valproate and carbamazepine are associated with a substantial risk of osteoporosis, but all three are efficient against partial seizures with or without secondary generalisation. Monotherapy is the main goal of epileptic treatment, and majority can be controlled on a single agent [32].

Carbamazepine, lamotrigine, sodium valproate and topiramate are the first-line AEDs recommended [33]. There is a good correlation between the dose and plasma concentration for carbamazepine (plasma therapeutic range 20–50 umol/l) [25]. Sometimes polytherapy may be necessary to control the seizures, and when used it should be used judiciously. Some antiepileptic drugs strongly induce hepatic enzymes (carbamazepine, phenytoin) [5], others the renally eliminated (gabapentin, pregabalin, vigabatrin, levetiracetam and topiramate) [34] have different modes of action, and still others take up an intermediate position; hence, they have therapeutic relevance [5]. Elderly patients are often on multiple drugs, and the use of AEDs that do not alter the metabolism of other drugs should be borne in mind. For example, neither gabapentin nor levetiracetam alters the metabolism of other drugs or is altered by other drugs [18]. Apart from the common side effects such as drowsiness, dizziness and mental slowing in the newer-

Table 1 Drug therapy in epilepsy

Older medications		
Drug	Daily dosage, range	Side effects
Phenytoin	Max: 600 mg/day	Ataxia, dizziness, motor, twitching, lymphadenopathy, marrow depression, osteoporosis
Carbamazepine	200–1200 mg	Dizziness, ataxia, drowsiness, bone marrow depression, osteoporosis, AV conduction delay and brady-arrhythmias
Valproate	Usual range 1–2 g/day	Nausea, vomiting, ataxia, rash
	Max:2.5 g/day	Hair loss, tremor, osteoporosis
New medications		
Gabapentin	1,200–3,600 mg/day	Skin rash, drowsiness, dizziness, weight gain, peripheral oedema, hepatotoxicity, impotence
Lamotrigine	100–300 mg/day	Skin rash, dizziness, nausea, vomiting, aggression, agitation, sedation, rash, ataxia, blurred vision, tremor
Topiramate	100–200 mg/day	Drowsiness, poor concentration and attention, depression, apathy, renal calculi
Levetiracetam	Up to 1,500 mg/bd	Anorexia, weight changes, mood changes, behavioural effects, drowsiness
Pregabalin	300–600 mg/day	Dry mouth, irritability, weight gain, pedal oedema, confusion, blurred vision
Oxcarbazepine	600–2,400 mg	Nausea, dizziness, fatigue leucopenia, hyponatraemia
Tiagabine	4 mg/day increasing	Change in mental status, somnolence, tremor, to 56 mg daily efficacy concerns, nervousness
Zonisamide	400–600 mg/day	Loss of weight, driving skills impaired, rashes including Steven-Johnson syndrome, renal stones

Information Sources: Beyenburg et al. [5], Walia et al. [35], Epilepsy Society [36]; Aust Prescr [37], Livertox [38]

generation antiepileptics, other side effects include skin rash, hepatotoxicity, weight gain, nephrolithiasis, angle-closure glaucoma, colitis and movement and behavioural disorders amongst others [35] (Table 1).

Impact

Epilepsy in the elderly is high, and this will continue to rise [39] in view of the rapidly growing elderly population especially the very elderly [30, 31, 39]. The impact and burden of epilepsy will continue to rise as the population ages [40]. Compared with their younger counterparts, the elderly experience a decline in their quality of life. There is high prevalence of comorbidities in the elderly. Patients with epilepsy have neuropsychological impairments including emotional distress, behavioural disorders and social isolation, and the quality of life is affected by the patients' perception of their disease more than actual seizure activity [41] (Boxes 1 and 2).

Box 1 Key Points Epilepsy in the Elderly

A cause can be identified in more than 60% of elderly people and is classified as remote symptomatic epilepsy [13].

Focal seizures occur at any age but most commonly after the age of 65 years [5].

Post-stroke seizures account for 30–40% of cases of epilepsy [10].

In a large series of patients with post-stroke seizures, 9% had status epilepticus [16].

In non-convulsive status epilepticus (NCSE), the patient presents with confusion and disordered sensorium [22].

Elderly persons with unexplained episodes of confusion, disorientation, decreased consciousness and motor or sensory symptoms should be evaluated for seizures, and an EEG- video monitoring should be considered.

(*continued*)

Box 1 Key Points Epilepsy in the Elderly (continued)

Seizures are more commonly associated with haemorrhagic rather than ischaemic stroke, and involvement of the cortex increases the risk.

In a large series of patients with post-stroke seizures, 9% had status epilepticus [16].

Periodic lateralising epileptiform discharges (PLEDs) have been commonly associated with cerebral infarction but also with other cerebral diseases such as encephalitis, tumour and demyelinating diseases [17]

MRI is more sensitive than CT. The limitations of EEG should be recognised.

Box 2 Key Points: Treatment of Epilepsy in the Elderly

Monotherapy is the main goal of epileptic treatment [32], and in the elderly, special consideration should be given to co-existing medical conditions and side effects.

Most elderly respond to antiepileptic drugs (AED) including low doses [29].

Generally there are no significant differences in the effectiveness of the AEDs if they are adequately used in relation to the type of seizure [5].

The newer drugs such as gabapentin, lamotrigine, oxcarbazepine, levetiracetam, tiagabine and topiramate appear to be better tolerated with regard to mood and cognitive effects.

Carbamazepine, lamotrigine, sodium valproate and topiramate are the first line of AEDs recommended.

In selecting a drug for the elderly, special consideration should be given to co-existing medical conditions [28].

Most elderly people respond well to AEDs including low doses of AED [29].

Box 2 Key Points: Treatment of Epilepsy in the Elderly (continued)

The elderly are very susceptible to adverse effects, and clear-cut consideration should be given to the most appropriate AED minimising its side effects and potential drug interactions.

Multiple Choice Questions

1. Which of the following hormones are used to determine whether a patient has had a recent seizure?
   A. ACTH
   B. Prolactin
   C. Serotonin
   D. Parathyroid hormone
2. The following are true regarding epilepsy in the elderly, except:
   A. Up to 70% of the seizures in the elderly are of the focal onset with or without secondary generalisation.
   B. Monotherapy is the main goal of epileptic treatment and in the elderly.
   C. Most elderly do not respond to antiepileptic drugs (AED) including high doses.
   D. The elderly are very susceptible to adverse effects.

MCQ Answers

1 = B; 2 = C

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Part VIII

Metabolic Bone Disorders in the Elderly

Part VIII provides information on some of the metabolic bone disorders which include osteoporosis, osteomalacia, and Paget's disease. It will highlight the improvements that have occurred in clinical care. It will discuss the pharmacological agents used in the treatment of these disorders with the main focus on their effects and adverse effects. Osteoporotic fractures that most commonly involve the vertebrae, proximal femur, and the wrists and vertebrals are two to three times as common as hip fractures. This review also discusses fractures as to their prevalence and in terms of costs, morbidity, and mortality. The incidence rates for hip fractures to projected populations in various parts of the world will rise from 1.66 million in 1990 to 6.26 million by 2050. One or more osteoporotic vertebral fractures were associated with increase in mortality. In the elderly, vitamin D deficiency is the most common cause of osteomalacia and most likely to inadequate dietary intake and in house bound or institutionalized elderly patients with little or no exposure to sunlight. Most patients with Paget's disease are asymptomatic. Symptomatic patients could present with bone pain, deformities and fractures, secondary osteoarthritis, and deafness.

Osteoporosis

43

Contents

Abstract

There is no one cause of osteoporosis, but a myriad of factors contribute to loss of bone, especially with aging in both men and women. Those with a family history of fractures or osteoporosis are at an increased risk, and the inheritability ranges from 25% to 80% for both fractures and for low bone mineral density. Dual-energy X-ray absorptiometry (DXA) has exceptional precision [8] or bone densitometry (BMD) are now available. Minimal trauma fractures (MTF) should be investigated for osteoporosis. It is recommended that vitamin D status be determined. Screening for secondary osteoporosis has yet to be proved to be cost-effective. It is recommended that vitamin D status be determined. Screening for secondary osteoporosis has yet to be proved to be cost-effective. Currently, the biphosphonates and denosumab are the mainstay of osteoporosis therapy [24] and biphosphonates orally or intravenously should be the first line of therapy especially in older patients [52]. This chapter will provide an update on the clinical management.

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_44

Keywords
Osteoporosis · Dual-energy X-ray absorptiometry (DXA) · Minimal trauma fractures (MTF) · Vitamin D status · Biphosphonates

Introduction

There is no one cause, but a myriad of factors contribute to loss of bone, especially with ageing in both men and women. Factors include sex hormones (oestrogen deficiency following menopause and in men decrease in testosterone levels), lifestyle factors such as diet, smoking, exercise, alcohol and low body weight and medications. Genetic make-up and at least 30 genes have been associated with development of osteoporosis [1]. It is a polygenic disorder resulting from the effects of several genes [2]. Non-modifiable risk factors for osteoporosis include family history, female sex, advanced age, history of fracture as an adult and European and Asian ancestry. White and Asian women are at greater risk [3]. Modifiable risk factors are shown in Box 1.

Box 1 Potentially Modifiable Risk Factors for Osteoporosis
Smoking and alcohol
Low calcium and vitamin D intake
Low body weight
Reduced or excessive physical activity
Poor health/frailty
Medications (steroids, barbiturates, proton pump inhibitors)

Osteoporosis can be classified as primary or secondary [3, 4]. Primary osteoporosis accounts for more than 95% of osteoporosis and is divided into type 1 and type 2. Type 1 occurs in women post menopause in whom the bone loss is accelerated over that produced for age and sex [3]. Type 2 is seen in older women or men over the age of 70 years and is usually associated with decreased bone formation [3]. Type 1 occurs within 15–20 years of menopause [5] with a peak incidence in the 60s and early 70s. In both types of osteoporosis, oestrogen deficiency has an important role for the pathogenesis in both men and women [6]. In men with osteoporosis 30% to 45% there is no identifiable cause [7]. Secondary osteoporosis or type 3 results from identifiable conditions [3] that may include metabolic and endocrine disease (hyperparathyroidism, hyperthyroidism, hypogonadism, diabetes mellitus), neoplasms, malnutrition, drugs (corticosteroids, phenytoin and heparin) and prolonged immobilization. Those with a family history of fractures or osteoporosis are at an increased risk, and the inheritability ranges from 25% to 80% for both fractures and for low bone mineral density (Box 2).

Box 2 Secondary Causes of Osteoporosis
Metabolic and endocrine
Hyperparathyroidism, hyperthyroidism
Hypogonadism in men, hyperprolactinaemia
Diabetes mellitus, chronic renal failure
Drugs
Corticosteroids, phenytoin, heparin, valproic acid
Other
Prolonged immobilization, inflammatory arthritis, hypervitaminosis A, malignancy, malnutrition
Information source: Iqbal [3]

Symptoms and Signs

Patients may be asymptomatic for years till fractures occur and the fractures may develop after minor or no apparent trauma. The common sites following falls are the wrists and hips. Subsequently muscle and bone pains occur especially in the back. Vertebral compression fractures occur in the weight-bearing vertebrae below the midthoracic region. The fractures may occur acutely with pain followed by amelioration of symptoms after a week or so but have residual pain over several months. Multiple compression vertebral fractures in the midthoracic region give rise to kyphosis (‘Dowager’s hump’).

Diagnosis

Standard X-rays are not very sensitive for diagnosing osteoporosis. Dual-energy X-ray absorptiometry (DXA) has exceptional precision [8], or bone densitometry (BMD) is now available, and BMD tests are now subsidized by Medicare for men and women 70 years or over. The World Health Organization devised an operational definition of osteoporosis [9]. The low bone density (or osteopenia) is defined by a bone mineral density >1SD but <2.5 SDs below the young normal mean. Women with bone density levels >2.5 SDs below the young-normal mean are considered to have osteoporosis [10]. If an individual with bone density below this threshold also has a fragility fracture, she fulfils the definition of established osteoporosis. Minimal trauma fractures (MTF) should be investigated for osteoporosis.

Bone density is reported as T- and Z-scores. T-score is the number of standard deviations away from the mean bone mass of a sex-matched young male. A T-score −1 and above indicates the bone density is normal, a score between −1 and −2.5 osteopenia and a score −2.5 and above likely osteoporosis [11]. Z-score is the number of standard deviations away from the mean bone mass of an age- and sex-matched control [11]. The spine may show osteoporosis earlier than the hip, but in the elderly the presence of osteoarthritis of the spine or aortic calcification may mask the presence of osteoporosis. Quantitative CT (QCT) scanning can produce similar measurements in the spine and hip. It isolates the trabecular or fast turnover bone and avoids measuring osteophytes.

Furthermore, it is recommended that vitamin D status be determined. Screening for secondary osteoporosis has yet to be proved to be cost-effective. However, it has been advocated that patients with osteoporosis should be evaluated for secondary causes with a basic biochemical screen including a full blood count, serum calcium, 25(OH) vitamin D, phosphatase and 24-h urinary calcium [12]. Other additional tests include PTH, thyroid-stimulating hormone, cortisol and serum and urine protein electrophoresis (Box 3).

Box 3 Further Testing Guided by Clinical Suspicion

Full blood count/ESR
- Serum calcium, creatinine, electrolytes
- Urinary calcium
- 25 (OH) vitamin D
- TSH
- Serum, urine electrophotogram
- Serum testosterone
- Parathyroid hormone (PTH)
- Liver function tests
- Antigliadin antibodies
- Small bowel biopsy

Levels of serum-free deoxypyridinoline (DPYR) or N-telopeptide cross links (NTX) or C-terminal telopeptide (CTX) may reflect type I collagen degradation [13]. If there is an excessive turnover, the levels are high, and conversely in reduced bone turnover, it is low. The levels are not sufficiently accurate for routine clinical use. The levels are subject to diurnal variation and are standardized to fasting, fasting morning levels for normal values [14]. The CTX test has been recommended to assess response to treatment and to monitor bone turnover in osteoporotics being treated with oral bisphosphonates. It gives an indication of the effects within 6 weeks when compared to BMD which requires about a year [14]. To predict the rate of bone loss and the resultant fracture risk, several metabolic markers, namely, serum NTX, TRAP-5b, BAP or urinary NTX, CTX and DPD, are used in clinical practice [15], and among the bone resorption markers, TRAP-5b might be outstanding as it is not affected by renal dysfunction or day-to-day variation [15].

Management

Prevention

Osteoporosis is a disease, and the main aim is the prevention of fractures by lifestyle advice (exercise, cessation of smoking, moderate consumption of alcohol) and medication and preventing falls in

patients with known or suspected osteoporosis. There is reliable evidence that calcium supplements with or without vitamin D do not prevent hip fractures although they marginally reduce total factures [16, 17]. Furthermore, calcium supplements increased the risk of renal calculi [17] and most likely increased the risk of myocardial infarction [18, 19] and have no role in the management of osteoporosis and general agreement is that calcium should be derived from the diet [20]. Vitamin D supplements have been shown to have no significant effects on either fracture rates [21] or bone density [22], and in fact high doses of vitamin D have shown increased fracture rates [23]. In osteoporosis management of those at risk, a daily supplement of 400–800 units would meet the requirements [24]. Smoking and excessive alcohol intake are to be avoided [25]. In the elderly with low bone density with or without fractures, pharmacological therapy should be considered. Specific interventions based on individual's risk factors should be set up to reduce risk of falls and number of fractures (Box 4).

Box 4 Prevention of Osteoporosis and Falls

Dietary – adequate vitamin D and dietary calcium

Lifestyle measures

Cease smoking

Moderating alcohol consumption

Increasing physical activity

Preventing falls

Assess personal aspects – visual defects, cognitive impairment, imbalance, etc.

Assess environmental factors

Review medications – hypnotics, potent hypotensives, drugs which cause osteoporosis (corticosteroids, antiepileptics). Pharmacological therapy to be considered

Treatment

Adequate nutrition – especially protein, calcium, phosphorus and vitamin D – is fundamental to any therapeutic programme [26]. Adequate calcium and vitamin D are required for osteoporotic treatments to act favourably, and vitamin D supplements may be used if diet is inadequate [27]. The pharmacological agents are broadly classed as antiresorptives and anabolics [26]. Several pharmacological agents including the bisphosphonates and selective oestrogen receptor modulator (raloxifene) have been shown to increase bone mass and to reduce fracture risk [8, 25]. Others are calcitonin and teriparatide [28, 29] (recombinant human PTH1–34) [30, 31], strontium ranelate and denosumab [32–34]. Despite the efficacy of the therapy, patients do not remain on the treatment for more than a year [30, 31].

Bisphosphonates

Bisphosphonates by inhibiting the enzyme farnesyl pyrophosphate synthase (FPPS) inhibit bone resorption through recruitment of osteoclasts, reducing activity and increasing apoptosis [35]. Randomized clinical trials have shown that bisphosphonates prevent primary and secondary hip and vertebral fractures by up to 40–60% [36–38]. Sodium alendronate (Fosamax) is the most often prescribed bisphosphonate and is taken 10 mg daily or 70 mg once a week, and risedronate (Actonel) is taken 5 mg a day or 35 mg once a week and ibandronate (Boniva) once a month. A recent innovation is vitamin D, and calcium has been incorporated with bisphosphonates. Fosamax Plus includes 2,800 units of vitamin D (a week supply). Actonel Combi in a special pack contains four tablets of Actonel 35 mg and six tablets X4 of calcium carbonate; each calcium tablet is 1250 mg. It is important to know that calcium supplement and bisphosphonates should not be taken together, and there should be an interval of 2 h apart for the absorption of one interferes with the other. It has been shown that bisphosphonates prevent fractures without calcium supplementation [39], and the efficacy of alendronate is not affected by calcium supplementation [40]. There have been reports of oesophagitis with alendronate therapy with ulceration or stricture confirmed by endoscopy in 26 of 52 patients with oesophagitis. With the exception of

gastrointestinal effects, bisphosphonates are well tolerated [41]. Zoledronic acid is a bisphosphonate with a hydroxyl group and imidazole side chain [42] and administered intravenously yearly [27]. Drug holidays have been recommended for individuals on bisphosphonates for the reason that the duration of action lasts for long periods after the cessation of the drug [24]. In the case of risedronate, 6–12 months for holiday and 1–2 years for alendronate have been suggested [24].

There is a strong association between bisphosphonates and osteonecrosis of the jaws (ONJ), but there is no evidence that bisphosphonates cause ONJ [14]. Individual risk factors include age (the older the person, the greater the risk), immunocompromised states (diabetes and corticosteroids) and dose and duration of oral bisphosphonates and are said to be rare before 3 years of weekly oral bisphosphonate treatment, and three quarters of the cases directly follow dental extraction. Other procedures such as deep periodontal scaling, trauma from dentures and dental implants have been identified [14]. CTX test can be used as an indicator of the risk of bisphosphonate-induced ONJ in patients with oral bisphosphonates [43]. If the level is <70 to 100 pg/ml, the risk of ONJ is highest; if the level is between 100 and 200, then the risk exists; and if the level is over 200 pg/ml, the risk of ONJ is rare [14].

Oestrogen Receptor Modulators

Raloxifene is a selective oestrogen receptor modulator (SERM) which prevents vertebral fracture [44]. Unlike oestrogen it does not stimulate the breast or uterus. It reduces the risk of breast cancer. An increased risk of venous thrombosis has been reported [45]. It alters lipoprotein profile [46] and decreases total and LDL cholesterol. It reduces the risk of vertebral and non-vertebral fractures in high-risk women [47]. The combination of SERM with oestrogen termed tissue-selective oestrogen complex (TSEC) reduces climacteric symptoms and preserves BMD [47].

Oestrogens

Hormonal replacement therapy although effective in primary prevention of fractures remains controversial because of uncommon but serious adverse effects in older women including stroke and breast cancer [48]. The use of oestrogen increases the risk of thromboembolism and endometrial cancer. The latter can be reduced in women with intact uterus by taking oestrogen with progestin to reduce the risk of endometrial cancer; however, taking oestrogen with progestin increases the risk of breast cancer, stroke, coronary heart disease and biliary disease. Oestrogen alone is safer than when combined with progestin and reduces breast cancer [41]. Transdermal preparation has been observed to lower venous thromboembolism compared to oral HRT. Treatment with HRT should be individualized.

Others
Strontium Ranelate

Strontium ranelate has recently been approved for treatment of postmenopausal osteoporosis with efficacy almost equivalent to the bisphosphonates [49]. Oral strontium ranelate belongs to a class of drugs called ‘dual-action bone agents’ (DABAs). Unlike the bisphosphonates it does not cause upper gastrointestinal side effects but has a slight increase in risk of venous thromboembolism [50]. It has proven efficacy especially in the prevention of vertebral fractures [51] and is appropriate in women who are unable to take bisphosphonates or cannot tolerate them [52]. It is administered as an oral powder at 2 g daily [27].

Teriparatide (Forteo)

Teriparatide is a human recombinant peptide of N-terminal fragment of human parathyroid hormone [30]. It is used in postmenopausal osteoporosis [31] and for treatment of primary or hypogonadal osteoporosis in men and in both men and women with glucocorticoid-induced osteoporosis [53]. It is administered subcutaneously at 20 mcg daily and it lacks long-term data [27].

Denosumab

Denosumab (Prolia) is a fully human IgG2 monoclonal antibody that neutralizes RANKL [33, 34] by inhibiting the binding of RANKL to RANK [32] in a similar way to osteoprotegerin [53]. It is administered subcutaneously 60 mg every 6 months but lacks long-term data [27, 47]. It is appropriate for women with high risk for fractures and who have had no beneficial effects with other therapies [52]. The most common adverse effects are headache, back pain, urinary tract infection, constipation, shoulder pain, arthralgia and nasopharyngitis [53].

Novel Agents

There are several novel agents that are in the late-stage clinical development. (1) Cathepsin K inhibitors. Cathepsin K, a lysosomal cysteine protease that is abundantly expressed in osteoclasts [54–56], is responsible for the degradation of bone matrix during bone remodelling process [55, 56]. Selective cathepsin K inhibitors have shown a promise as anti-resorptives in osteoporosis [55]. Odanacatib, a cathepsin K inhibitor, has been shown as a promising agent in postmenopausal osteoporosis [56, 57]. It is well tolerated and has a profile for once-a-week dosing [57]. It increased lumbar spine and total hip BMD in postmenopausal women with low BMD administered weekly over 2 years and was well tolerated [54]. (2) Novel anabolic agent abaloparatide (recombinant parathyroid hormone-related peptide) has anabolic activity like teriparatide [58, 59]. It is associated with an 86% reduction in vertebral facture incidence [59]. Romosozumab, a novel humanized monoclonal antibody that inhibits sclerosin, an osteocyte-derived inhibitor of osteoblastic activity has a dual effect of promoting bone formation and inhibiting resorption [60].

PTH although effective is of limited use because of the cost. Salmon calcitonin is less effective than bisphosphonates. Testosterone is effective in increasing bone density in hypogonadal men, but in one study it had not been large enough to have had any effect on fracture rate [61], but men with osteoporosis and hypogonadism should be treated with testosterone. Vitamin D is used for both prevention and treatment of the deficiency. HRT is not recommended in females for fracture risk reduction alone. It should be prescribed for the prevention of osteoporosis only if moderate to severe menopausal symptoms, hot flushes and night sweats are present. The rigorously investigated drugs reported are the bisphosphonates (alendronate, risedronate, zoledronic acid), denosumab, the selective oestrogen receptor modulator (SERM) (raloxifene), the anabolic agent teriparatide and strontium ranelate. Currently the bisphosphonates and denosumab are the mainstay of osteoporosis therapy [24], and bisphosphonates orally or intravenously should be the first line of therapy especially in older patients [52]. The delivery systems have now advanced that allow treatment to be administered daily, weekly, monthly and annually either by mouth or intravenously [41]. Denosumab is appropriate for women at high fracture risk or who have failed other therapies [52]. For younger postmenopausal women who are at greater risk of for vertebral than hip fractures, selective oestrogen receptor modulators should be considered [52]. Hip protectors have been reported to reduce fractures in the elderly people in institutions.

Osteoporosis in Men

In Australia 31% of men and 50% of women over the age of 60 years will sustain a fragility fracture due to osteoporosis throughout their remaining lifetime [62].

Corticosteroid-Induced Osteoporosis (CIOP)

Patients on corticosteroid therapy are at increased risk of sustaining fractures. Long-term treatment with corticosteroids reduces bone formation by promoting osteoblast and osteocyte apoptosis. There is decreased osteoblast renewal with osteoblast inhibition resulting in decreased amount of bone replaced in each remodelling cycle [63]. Other factors in the development of corticosteroid-induced osteoporosis (CIOP) are in the calcium-regulating mechanisms. Intestinal absorption of calcium is reduced [64] and also leads to reduced renal tubular

reabsorption [65]. In a cross-sectional study in Nottinghamshire, 65,000 patients were taking oral corticosteroids, that is, 0.5%. The mean dose was 8 mg/day and median duration of treatment was for 3 years. They were aged 60–80 years. It was noted that only 14% were taking prevention treatment for osteoporosis [66].

A number of agents such as calcium, activated vitamin D, HRT and fluoride have been used with variable effectiveness in the prevention and treatment of CIOP. Teriparatide and bisphosphonates have been shown to be fully effective in CIOP [26]. The active metabolite of vitamin D3 such as calcitriol may effectively slow the rapid bone loss in patients starting on corticosteroids [63]. Bisphosphonates are very effective in the primary and secondary prevention of CIOP. Cyclical etidronate and alendronate have shown in a double-blind study positive effects on bone mineral density in the lumbar spine, hip and fewer vertebral fractures in postmenopausal women [67, 68].

Impact

According to the World Health Organization, there is a variation in the incidence and prevalence of osteoporosis, and 1 in 3 women and 1 in 12 men over the age of 50 years worldwide have osteoporosis, and it is a major public health problem [69]. It affects people of all ethnic backgrounds [8]. In Australia it is estimated that 60% of women and 30% men over the age of 60 years will suffer osteoporotic fracture in their remaining lifetime [62], that is, one in two women and one in three men will have a minimal trauma fracture (MTF) because of osteoporosis. In the United States, 26% of women aged 65 years or more and 50% of women aged 85 years and/or more have osteoporosis [28] and are responsible for more than 1.5 million fractures per year [70].

The quality of life is affected by the fractures which are associated with pain and decreased physical, social and psychological incapacity [71, 72]. In the older patient, QoL depends on comorbidity, mobility and independence for activities of daily living (ADLs) [71]. Only 25% of individuals with hip fracture return to their ADLs [73]. The incidence of MTF increases with increasing age of the population, and there were 16,000 fractures in 1966 [74], and the financial costs for all these fractures are $1.9 billion per year [75]. In the United States, nearly $9 billion were spent in 1995 for the management of hip fractures [76]. The impact of fracture on the health-related quality of life is profound, and about 25% of the patients reside in long-term care facilities for a year or more after fracture [76]. With the world's population ageing, hip fractures are becoming more frequent and are increasing by 1–3% per year [77]. Men have a 13% lifetime risk of fracture which is associated with significant functional impairment and increased mortality [78] (Boxes 5 and 6).

Box 5 Treatment Summary

Women with early postmenopause and older postmenopause with or without fractures	Alendronate
	Raloxifene
	Active vitamin D compounds
Men with hypogonadism testosterone idiopathic	Bisphosphonate
	Calcium supplementation
	Elderly (house bound or in institutions) simple vitamin D supplements

Information source: Sambrook and Eisman [79]

Box 6 Key Points. Osteoporosis

One in 3 women and 1 in 12 men worldwide have osteoporosis.

One in two women and one in three with MTF will suffer fractures because of osteoporosis.

There is no one cause, but a myriad of factors contribute to loss of bone.

(*continued*)

Box 6 Key Points. Osteoporosis (continued)

It is a polygenic disorder resulting from the effects of several genes [2].

Primary osteoporosis accounts for 95% of osteoporosis and is the form seen in older persons and postmenopausal women (Box 5).

Patients may be asymptomatic for years till fractures occur.

MTF should be investigated for osteoporosis.

Screening for secondary osteoporosis has yet to be proved to be cost-effective.

The rigorously investigated drugs reported are the bisphosphonates (alendronate, risedronate), denosumab, the selective oestrogen receptor modulator raloxifene, the anabolic agent teriparatide and more recently strontium ranelate.

Prior to starting raloxifene and strontium ranelate, assess risk of cardiovascular events.

Osteoporosis in men although very common is less well known than osteoporosis in women.

Patients on corticosteroids are at increasing risk of sustaining fractures.

Multiple Choice Questions

1. A 72-year-old woman with osteoporosis developed severe low back pain following attempting to move a heavy chair. The X-ray of the lumber spine showed osteoporosis, 'fish vertebrae' and a compression fracture of L3. What is the appropriate initial treatment?
   A. Calcitonin for 4 weeks
   B. Bed rest and bracing
   C. Analgesics
   D. Vertebroplasty
2. Typical features of osteoporosis are:
   A. Asymptomatic ('silent disease') till fracture occurs.
   B. One in three women and one in three men would have osteoporosis worldwide.
   C. Serum calcium, phosphorus and alkaline phosphatase levels are raised.
   D. It is a typical complication of Addison's disease.

MCQ Answers

1 = C; 2 = A

Extending Matching Questions

A. Osteoporosis
B. Multiple myelomatosis
C. Prolapsed intervertebral disc
D. Paget's disease
E. Metastasis from prostate cancer
F. Osteomalacia
G. Lumbosacral strain

The following patients have in common low back pain of acute onset. Choose the most likely diagnosis from the list above. Each option can be used only once.

1. An 80-year-old woman in a nursing care facility has difficulty in climbing stairs and standing. She developed severe low back pain following a fall. Her serum calcium is low and alkaline phosphatase raised. X-ray of the spine showed biconcave appearance of 'fish vertebra' and translucent bone texture. There were pseudofractures in the pelvis.
2. A 75-year-old man was seen with sudden onset of low back pain. His medical history includes a long-standing lower urinary tract symptom. The serum alkaline phosphatase is elevated. X-ray of the spine showed homogenous sclerosis of the vertebrae.
3. A 65-year-old man developed severe low back pain. His ESR was markedly elevated and blood smear showed rouleaux formation. X-ray of the spine showed osteolytic foci – 'moth eaten' in the vertebrae.
4. A 75-year-old suddenly developed severe pain in his back. The alkaline phosphatase was elevated. X-ray of the spine showed framed sclerosis with coarse trabeculae of the vertebrae.

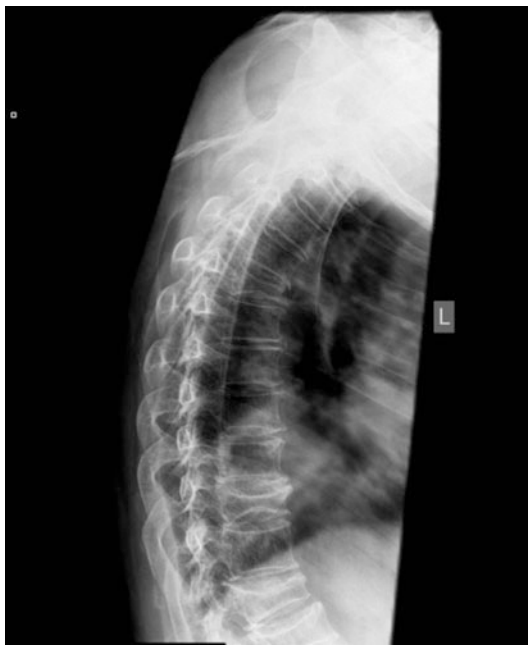
5. A 67-year-old woman developed severe low back pain following an attempt to lift a heavy object. The serum calcium and alkaline levels were normal. X-ray of the spine showed the bone texture of the vertebrae to be radiolucent, biconcave appearance of 'fish vertebrae' and a compressed fracture of L3.

   Compressed fracture of T10 secondary to osteoporosis.
   1. Lifestyle changes
   2. Pain relief with analgesics
   3. Bisphosphonates
   4. Prevention of falls

EMQ Answers

1 = F; 2 = E; 3 = B; 4 = D; 5 = A

Case Scenario



1. A 72-year-old woman presents with sudden severe pain in the back while lifting her granddaughter.

   BMD done 2 months ago revealed a T-score below −2.5 SD. X-ray is shown.

   What does the X-ray show?

   What is the cause?

   State briefly the management.

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Osteomalacia

44

Contents

Abstract

In the elderly, vitamin D deficiency is the most common cause and most likely due to inadequate dietary intake and in house-bound or institutionalised elderly patients with little or no exposure to sunlight. In the adults, the clinical significance of vitamin D deficiency may be subtle and overlooked and the patient being asymptomatic. X-rays show reduction in the skeletal density which is difficult to distinguish from osteoporosis. The changes in calcium, phosphate, ALP and 25(OH) D_3 levels together with radiographic changes will help in making a diagnosis. There is general agreement that the vitamin 25 D level should be more than 50 nml/L, although some have suggested a threshold level of 60–70 nmol/L.

Keywords

Osteomalacia · Vitamin D deficiency · Exposure to sunlight · Fractures

Introduction

It occurs worldwide, but it is rare in the United States approximating 1 in 1,000 [1]. It is often subclinical. In a study of 26 cases with fracture of the proximal end of the femur, 65% had subclinical osteomalacia [2]. In the elderly, vitamin D deficiency is the most common cause (Box 1) and most likely due to inadequate dietary intake [3] and in house-bound or institutionalised elderly patients with little or no exposure to sunlight [4]. Other causes include malabsorption of calcium, phosphate and/or vitamin due to gastrointestinal disease.

Box 1 Causes of Osteomalacia

i. Dietary deficiency of vitamin D.
ii. Lack of exposure to sunlight.
iii. Malabsorption syndrome.

(*continued*)

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_45

Box 1 Causes of Osteomalacia (continued)

iv. Hepatic disease.
v. Renal osteodystrophy in chronic renal failure results from vitamin D metabolism, parathyroid function and abnormalities in acid-base balance.
vi. Hypophosphataemia.
vii. Anticonvulsant therapy – phenytoin, phenobarbitone.
viii. Hypoparathyroidism, pseudohypoparathyroidism.

Symptoms and Signs

In the adults, the clinical significance of vitamin D deficiency may be subtle and overlooked and the patient being asymptomatic. There may be muscle weakness and fits. Bone pain is the hallmark and this may be diffuse with proximal muscle weakness and aggravated by movement. There is difficulty in going upstairs and rising from the chair. Muscle atrophy has been described [5, 6]. Vitamin deficiency especially in the elderly increases the risk of falls and fractures [7]. Box 2 shows the signs and symptoms.

Box 2 Signs and Symptoms in Osteomalacia

Pain – localised or generalised
Bones – vertebrae, ribs, hips, legs
Deformities – lower leg bowing, gibbus deformities
Fractures – vetebrae, wedge/crush fractures

Radiological Findings

X-rays show reduction in the skeletal density which is difficult to distinguish from osteoporosis and vertebral biconcavity with compression fractures. Occasionally thin longitudinal bands of radiolucency may appear in the pelvis (trefoil pelvis), ribs, long bones (in the femur – protrusio acetabuli), scapulae and vertebrae (biconcave vertebrae). The only findings that are distinctive for osteomalacia are the Looser's fractures. They are extremely uncommon and tend to occur in the pelvis and scapulae (Looser's zones) and are said to be due to stress fractures. Multiple bilateral and symmetrical pseudofractures in patients with osteomalacia are called Milkman's syndrome. The differential diagnoses in the radiological appearances include hyperparathyroidism, postmenopausal osteoporosis, osteoporosis of thyrotoxicosis, multiple myeloma and Cushing's disease.

Diagnosis

The changes in calcium, phosphate, ALP and 25 (OH) D_3 levels together with radiographic changes will help in making a diagnosis.

Treatment

The purpose of the treatment is to prevent hypocalcaemia which may result in cataract and seizures and to prevent skeletal deformities. Adequate calcium and phosphate intake together with vitamin D 40 μg (1,600 IU) daily and monitoring urine, serum levels of calcium and vitamin D are recommended. There is general agreement that the vitamin 25 D level should be more than 50 nml/L, although some have suggested a threshold level of 60–70 nmol/L [8]. With moderate to severe vitamin D deficiency, a regimen of 4,000 IU/day for 3–4 months may be required and ensures that serum 25(OH) D concentrations exceed 100 nmol/L [9]. In the elderly, fracture prevention studies have shown that vitamin D dose of 500 IU/day with calcium 1,000/day could achieve this [10]. Report of vitamin D toxicity is rare. Vitamin D toxicity with hypercalcaemia involves an intake of >1,000 μg (40,000 IU/day) [9]. Vitamin D3 is preferable to

vitamin D2 as it is more effective [11]. Serum 25 (OH) D_3 and 1.25$(OH)_2$ D_3 will rise in 1–2 days and serum phosphatase in 10 days. Vitamin D and calcium supplements are strongly recommended for household and institutionalised elderly patients who are at highest risk of vitamin D deficiency. Vitamin D is obtained from the diet (D_2) and is absorbed in the upper small bowel. The precursor D_3 is synthesised from 7-dihydrocholesterol in the skin after exposure to sunlight and is then isomerised to D_3. The D3 is then converted to 25 ()H) D3 in the liver and in the kidneys to its much more metabolically active form, 1.25$(OH)_2$ D_3.(calcitriol). Vitamin D is predominantly manufactured in the skin from absorption of UV light. Sun exposure alone would be enough for most people to maintain adequate vitamin levels (Box 3). The main nutritional sources include liver, eggs, oily fish (salmon, herring) and some fortified foods such as margarine and some low-fat milk. Vitamin D increases the calcium absorption, enhances resorption by the kidney tubules, stimulates osteoblasts to produce alkaline phosphatase and inhibits parathyroid hormone secretion. Vitamin D with or without calcium contributes to muscle strength and improves balance and navigation abilities and decreases risk of falls [7].

Box 3 Sun Exposure

Expose hands, face and arms to sunlight, midday for 5–10 min in summer.

In winter to increase to about 30 min.

Dark-skinned people require longer exposures.

Impact

Bone pain is the hallmark of osteomalacia, and this may be diffuse with proximal muscle weakness and aggravated by movement. There is difficulty in going upstairs and rising from the chair, and it interferes with walking. There is muscle atrophy. Compression fractures occur with loss of height (Box 4).

Box 4 Key Points. Osteomalacia

Osteomalacia occurs in the elderly with poor nutrition [3] and in institutionalised patients [4].

Bone pain is the hallmark with proximal muscle weakness.

X-rays show reduction in skeletal density which is often difficult to distinguish from osteoporosis.

The only distinctive findings on X-ray are the Looser's fractures.

There is general agreement that the vitamin 25 D level should be more than 50 nml/L, although some have suggested a threshold level of 60–70 nmol/L[8].

Vitamin D and calcium supplements are strongly recommended for household and institutionalised elderly patients who are at highest risk of vitamin D deficiency.

Multiple Choice Questions

1. A 75-year-old woman in a nursing care facility has osteomalacia. The following are true EXCEPT:
   A. Proximal myopathy.
   B. Serum calcium is low and alkaline phosphatase level is raised.
   C. Pain only after fracture.
   D. Vitamin D deficiency is an important cause.

MCQ Answers

1 = C

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Paget's Disease

45

Contents

Abstract

Paget's disease usually occurs past middle age with increasing frequency with age. It is often detected as an incidental finding by an X-ray or an elevated alkaline phosphatase level or when being investigated for another disorder. Most patients are asymptomatic. Symptomatic patients could present with bone pain, deformities and fractures, secondary osteoarthritis and deafness. Pagetic lesions are extremely vascular with increased blood flow, increased blood volume, high cardiac output together with cardiomegaly, left ventricular hypertrophy and cardiac failure.

Keywords

Paget's disease · Bone pain · Deformities and fractures · Secondary osteoarthritis · Deafness · Urinary hydroxyproline

Introduction

Paget's disease usually occurs past middle age [1] with increasing frequency with age [2]. It occurs in about 4% of Australians over the age of 55 years [3]. Both men and women are affected, but it is more prevalent in men than in women [2]. In the United Kingdom the incidence rate was found to be 5 per 10,000 person years among men and 3 per 10,000 person years in women over a period between 1988 and 1999 [2]. There is a geographic variation in its prevalence [1]. It is prevalent in England, Europe, Australia, New Zealand, South Africa and the United States [2] with highest rates in the United Kingdom [1]. It is uncommon in Scandinavia, Japan [4], China and India [3]. The overall prevalence in the Caucasians is about 3% [1], and in Japan in the 55 years old and over, it is 0.41/100,000 [4].

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_43

Clinical Manifestations

It is often detected as an incidental finding by an X-ray or an elevated alkaline phosphatase level or when being investigated for another disorder. Most patients are asymptomatic [1, 5]. The symptomatic patients present with several signs and symptoms which include skeletal, neuromuscular and cardiovascular complications. Symptomatic patients could present with bone pain, deformities and fractures [5], secondary osteoarthritis and deafness [6]. Pain is due to the lytic activity, to the fractures or to the arthritic changes that are often associated with Paget's disease. Fractures may occur in the long bones or vertebrae and usually follow minor trauma. Common sites of the fractures are the femur and tibia and in the lumbar and sacral regions. In the vertebrae crush or wedge fractures may be heralded by back pain. Deformities give rise to an enlarged skull, and in the weight-bearing bones, tibia and femur bowing and acetabular deformities could also develop.

Neurological complications are largely due to compression of the nerves. Paget's disease of the skull could affect any of the cranial nerves [3]. Involvement of the VIII cranial could give rise to bilateral or unilateral nerve deafness which may be conductive, sensorineural or mixed [3]. Optic atrophy and papilloedema can be due to either increased intracranial pressure or compression of the nerve at the optic foramen [7, 8]. Brain stem compression from basilar invagination [3] can cause hydrocephalus [9]. Other unusual neurologic syndromes include cerebellar dysfunction, myelopathies, cauda equina syndrome and radiculopathies [9].

Pagetic lesions are extremely vascular with increased blood flow, increased blood volume, high cardiac output together with cardiomegaly, left ventricular hypertrophy and cardiac failure [10, 11] especially in patients with extreme skeletal involvement [12]. Paget's disease has a genetic component possibly linked to an osteosarcoma tumour-suppressor gene in the chromosome 18 region [13]. Osteogenic sarcoma may occur in less than 1% of the cases [3, 9, 14]. Degenerative joint disease due to hypertrophy of the subchondral bone involves especially the knees and ankles (Box 1).

Box 1 Clinical Manifestations of Paget's Disease

I. Skeletal
- Pain – low back, headache
- Deformities – thickening and bowing, large skull, kyphosis
- Fractures – complete/fissure fractures
- Vertebral compression
- Neoplastic – sarcomatous changes
- Degenerative joint disease

II. Neurological
- Cranial nerves
  - VIII – deafness
  - II – optic atrophy, papilloedema
  - VII – Bell's palsy
- Medulla and cerebellum
  - Double vision, dysarthria
  - Dysphagia
- Spinal cord
  - **Paraparesis, loss of sphincter** control
  - Radiculopathy
  - Muscle weakness, sensory loss
  - Sphincter abnormalities
- Peripheral nerves
  - Carpal, tarsal entrapment

III. Cardiovascular
- High output failure
- Cardiovascular calcification
- Warmth of overlying skin

Information sources: Abelson [6]; Poncelet [9]; Bone [12]

Laboratory Findings

Serum alkaline phosphatase (ALP) is elevated in 85% of individuals with untreated Paget's disease [1] and is due to increased osteoblastic activity. The urinary hydroxyproline excretion is increased sometimes markedly up to more than 20 times the normal and is a measure of bone resorption. Hypercalcaemia is rarely seen but can be precipitated by immobilization or by malignancy. Serum phosphate is sometimes erroneously recorded as slightly high. Hyperuricaemia and gout are observed frequently in patients with Paget' disease.

Radiological changes are most commonly evident in the skull, pelvis and femur. Earliest changes on the X-ray are osteolytic lesions which may be seen in the affected long bones. This is followed by mixed osteolytic and sclerotic lesions, and lastly sclerotic lesions predominate with bone enlargement. Bone scans using radionuclide technetium or radionuclide bisphosphonate demonstrate increased uptake areas which are difficult to see in standard X-rays (Fig. 1).

Diagnosis

Diagnosis is fairly easy with the suggestive signs and symptoms, radiological changes and elevated levels of ALP and urinary hydroxyproline. Urinary levels of N-telopeptide, hydroxyproline and deoxypyridinoline are better measures of bone resorption and useful in the diagnosis of Paget's disease [15]. Vitamin D and calcium supplements are strongly recommended for household and institutionalized elderly patients who are at highest risk of vitamin D deficiency. In cases of minimal involvement, they can all be negative with only a positive scan. The UK guidelines in the management of Paget's disease of bone recommended that all patients with Paget's disease should have a scintigraphy to determine the extent of skeletal involvement [16]. According to Scarsbrook et al. [17] whilst scintigraphy is more sensitive than radiography, the difference between the two in detecting sites of disease has been overstated. They cited several reports in support and felt that overall use of scintigraphy should be discouraged reasons in terms of expense as well as radiation exposure.

Treatment

The asymptomatic patients with minimal bone involvement require no treatment, and about three-quarters of the patients are only of minor consequence, and all they need is reassurance with close observation. As the bone involvement gets more extensive, treatment is instituted to prevent complications. Box 2 shows the main indications for commencement of drug treatment.

Box 2 Indications for Drug Therapy

Severe pain in both bone and joint.

In Neural compression, prevents and relieves complications, e.g. neurological deficits, fractures and hearing loss.

Prior to elective surgery at an active Pagetic site to reduce intraoperative blood loss.

Presence of disease activity in asymptomatic patients at sites to prevent future complications.

(*continued*)

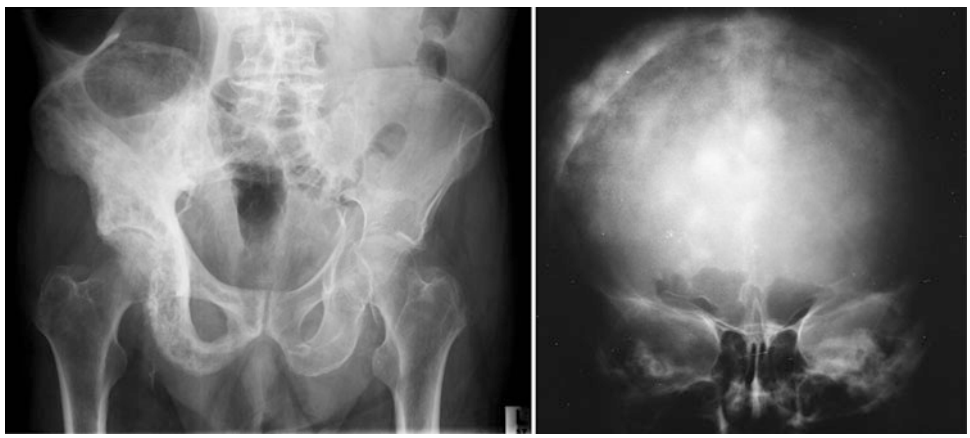

Fig. 1 Shows broadened skull, loss of tables and 'cotton ball' appearance in Paget's disease

Box 2 Indications for Drug Therapy (continued)

Prevent progression of skeletal involvement.

Preparation for orthopaedic surgery.

Marked elevation of biochemical parameters.

Prevent cardiovascular complications.

Information sources: Walsh [3], Scarsbrook et al. [17], Siris et al. [18]

Drug Treatment

The bisphosphonate therapy influences ion influxes and suppresses bone resorption. They inhibit the osteoclastic activity and do not compromise mineralization and are the treatment of choice in most patients with Paget's disease. Several studies have shown that second- and third-generation bisphosphonates such as alendronate, risedronate and tiludronate are effective in inhibiting bone turnover in patients with Paget's disease [19]. They are effective in controlling pain and are well tolerated [19]. Both alendronate and risedronate are effective in normalizing ALP in about half the cases. Alendronate is conventionally prescribed as a 6-week treatment course [16, 20, 21]. Alendronate must be taken on an empty stomach about 30–120 min before food, drink or medications containing calcium, iron and magnesium or aluminium-containing salts as absorption is impaired. Failure to abide by this will reduce their effectiveness. Both have a risk of gastrointestinal mucosal injury. They can cause severe oesophageal erosions and ulcers. To minimize these adverse effects, they should be taken with a full glass of water with patient in an upright position, remaining upright for at least 30 min. The duration of therapy with alendronate is 6 months and in the case of risedronate 2 months [3, 22]. Larger doses may interfere with bone mineralization and decrease osteoblastic activity. They may lower serum calcium and may require calcium and vitamin D supplements. They are not the preferred treatment for elective orthopaedic surgery. There are limitations to oral therapy [5].

Pamidronate given intravenously is of benefit and efficacious, and the recommended dose is a single dose of 60 mg IV in mild cases or two to four doses/day or weeks apart for more severe cases [23]. Recent studies have demonstrated that single infusion of 5 mg of zoledronic acid normalized the serum alkaline phosphatase in 89% of the patients and a prolonged biochemical remission [24]. Two other double-blind 6-month trials with one-time intravenous 5 mg zoledronic acid achieved a therapeutic response in 96% of the patients compared to 74% treated for 60 days with risedronate 30 mg orally [5].

Calcitonin is now used in settings when second-generation bisphosphonates are poorly tolerated or are not available. It heals osteolytic lesions and is the preferred treatment before orthopaedic surgery. Side effects are usually mild, nausea and facial flushing [25] (and regresses as treatment continues). In patients resistant to salmon calcitonin, human calcitonin appears to be effective. Therapy with calcitonin can be discontinued after 6–12 months and restarted when relapse occurs. Calcitonin can be given as a nasal spray [25, 26]. Prior to commencement of drug therapy, two baseline ALP levels are determined and drug treatment continued till remission is reached. In patients with Paget's disease, during chronic treatment with salmon calcitonin, ALP activity and urinary hydroxyproline excretion decrease on an average of 50% [25].

Impact

Most patients are asymptomatic [1, 5]. The symptomatic patients present with several signs and symptoms which include skeletal, neuromuscular and cardiovascular complications. Patients with Paget's disease suffer from pain and may suffer from fractures and nerve damage. Involvement of the VIII may result in deafness. Pagetic lesions are extremely vascular with increased blood flow, increased blood volume, high cardiac output together with cardiomegaly, left ventricular

hypertrophy and cardiac failure [10, 11]. Osteogenic sarcoma may occur in less than 1% of the cases [3, 9, 14]. Depending on the severity of the disease, the functional status may be affected (Box 3).

Box 3 Key Points. Paget's Disease

It is often detected as an incidental finding by an X-ray or an elevated alkaline phosphatase.

Symptomatic patients could present with bone pain, deformities and fractures.

Neurological complications are largely due to compression of the nerves.

Pagetic lesions are extremely vascular with increased blood flow, high cardiac output, left ventricular hypertrophy and cardiac failure.

Osteogenic sarcoma may occur in 1% of the cases.

Urinary hydroxyproline is increased.

Urinary levels of N-telopeptide and pyridinoline are better measures of bone resorption.

Multiple Choice Questions

1. The following are true of Paget's disease, EXCEPT:
   A. It is uncommon in Japan, China, India and Scandinavia.
   B. Genetic factors do play a role.
   C. Serum alkaline phosphatase is increased and so is urinary hydroxyproline.
   D. Elderly patients always present with severe bone pain.
2. The following neurological manifestations of Paget's disease are true, EXCEPT:
   A. Deafness
   B. Bell's palsy
   C. Paraparesis
   D. Peripheral neuropathy
3. The following are true of Paget's disease EXCEPT:
   A. Osteogenic sarcomas occur in 1% of the patients with Paget's disease.
   B. Hypercalcaemia occurs commonly.
   C. On X-ray the skull is thickened and may have a 'cotton wool' appearance
   D. Hyperuricaemia and gout are observed frequently in patients with Paget's disease.
4. The following are true in the treatment of Paget's disease, EXCEPT:
   A. Treatment can be deferred in asymptomatic patients with minimal bone changes.
   B. Treatment initially with either oral or parenteral bisphosphonate which has little toxicity.
   C. Calcitonin can be used as a nasal spray.
   D. Larger doses of bisphosphonate do not interfere with bone mineralization or decrease osteoblastic activity.

MCQ Answers

1 = D; 2 = D; 3 = B; 4 = D

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Osteoporotic Fracture and Management

46

Contents

Abstract

The chapter provides an overview of osteoporotic fractures occurring in the hip and vertebrae, the prevalence and clinical manifestations with the main focus on their effects. Osteoporotic fractures most commonly involve the vertebrae, the proximal femur and the wrists, and vertebrals are two to three times as common as hip fractures. The past few decades have seen an increasing number of hip fractures worldwide, and this trend will continue with the increase in the elderly population. The femoral neck has little cancellous bone, and the blood supply is poor and often results in complications. The intertrochanteric region consists largely of cancellous bone with good blood supply with different treatment, complications and mortality. Majority of the patients with vertebral fractures are treated conservatively. Kyphoplasty has also been shown to reduce pain and restore vertebral body height. Sacral insufficiency fractures are often mistaken both clinically and radiologically with metastatic disease.

Keywords

Osteoporotic fractures · Hip fractures · Vertebral fractures · Sacral insufficiency fractures · Kyphoplasty · Vertebroplasty

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_46

Hip Fractures

Introduction

Hip fractures are defined as fractures occurring in the regions of the head, neck and proximal part of the femur. Both cortical and trabecular bones undergo a continuous process of structural remodelling, and an imbalance in this process results in changes in the skeletal microarchitecture [1]. The trabecular bone is more active and more subject to bone turnover and to remodelling. The disruption of the microarchitecture in trabecular bone, decreased density and changed bone material quality lead to bone fragility [2]. The fracture sites in osteoporosis, the wrist, the hip and the vertebra, have relatively high trabecular bone-to-cortical bone ratio, and these areas rely on trabecular bone for strength [3].

The past few decades have seen an increasing number of hip fractures worldwide, and this trend will continue with the increase in the elderly population. With the increase in life expectancy, the older people will constitute a large portion of those afflicted with hip fracture. In 1990, there was an estimated 1.66 million hip fractures worldwide [4], and this largely occurred in Europe and North America [5]. Several studies have indicated geographic disparities in the incidence rates. In countries of Asia, Africa and South America, the incidence rates are lower [6]. The incidence rates for hip fractures to projected populations in various parts of the world will rise from 1.66 million in 1990 to 6.26 million by 2050 [6]. The number of hip fractures however will fall from half to quarter in 2050 in Europe and North America but will rise in Asia and Latin America [4] and will account for over 70% of the projected 6.26 million in the year 2050 [5]. This rise is due to the continued growth of the elderly population in these countries [6].

Comparisons of hip fracture incidence within countries and communities and between countries are useful to identify high-risk populations. The highest incidence has been reported in white Scandinavians and North Americans [4]. In the whites, there is a female preponderance, while in the blacks and Asians, it is the reverse [7], and the lifetime risk of hip fracture is 16–18% in white women and 5% in white men [4]. In the United States, femoral neck and intertrochanteric fractures occur with almost the same frequency in patients between the ages of 65 and 99 years [8]. In the elderly, changes in stability, balance, gait disorder, muscle strength and co-morbidities such as cognitive impairment are precipitating factors for falls [9]. Studies have shown that postural sway, cognition and behavioural deficits and moderate to severe disability are common to patients who fall [10]. Muscle strength decreases approximately by 50% from age 30 to 80 years, and the amount of body sway increases with reduction of proprioception [9].

Clinical Manifestations

Pain with marked limitation of movement is the mode of presentation. There is extreme tenderness on palpation. All movements are extremely painful except in rare cases of impacted fractures. The leg is held in adduction with external rotation. The differential diagnosis is from dislocations. In anterior dislocation the leg is flexed, externally rotated and abducted and the head of the femur can be felt in the groin. In posterior dislocation the leg is flexed adducted and internally rotated. Broadly fracture of the neck of the femur can be grouped as intracapsular and extracapsular. The former includes subtypes subcapital, transcervical and basal and the latter into intertrochanteric and subtrochanteric. The femoral neck has little cancellous bone and the blood supply is poor and often results in complications [11]. The intertrochanteric region consists largely of cancellous bone with good blood supply [11] with different treatment, complications and mortality.

Vertebral Fractures

Introduction

The incidence of vertebral fracture is assessed by a 20–25% reduction in the vertebral height (anterior, posterior and middle) [12]. Osteoporotic fractures most commonly involve the vertebrae, the proximal femur and the wrists [13], and vertebrals are two to three times as common as hip fractures [14]. Considering all osteoporotic fractures, 46%

of the fractures are vertebral, 16% hip and 10% the wrists [15]. It is difficult to quantify the incidence of vertebral fractures because only one third come up for medical attention [16] and only 2–10% are hospitalised [14, 17, 18].

In Europe based on morphometric fractures, the age-standardised incidence was 10.7 and 5.7 per 1,000 person years in women and men, respectively [19]. The overall prevalence ranged from 10 to 25% in women and 10–27% in men based on population studies [20–23]. The incidence of symptomatic vertebral fractures was 0.2 per 1,000 person years in patients under 45 years, and this increased to 1.2 per 1,000 person years after 85 years [24]. The incidence of vertebral fractures increases with age in both men and women, and in both the common type of fracture was the wedge-shaped fracture [25]. Based on radiological criteria, the prevalence was found to increase by 12% in both men and women [26], and the closeness was attributed to associated trauma in men [27].

One or more osteoporotic vertebral fractures were associated with increase in mortality [28–30]. One in five patients with incident vertebral fracture will experience a further vertebral fracture within a year [16, 30]. In women the prevalence of vertebral fracture increases with age from 20% in the 50-year-old menopausal women to 64.5% in older women [30].

Clinical Manifestations

Acute pain is the commonest form of presentation. Other symptoms include postural changes, loss of height including kyphosis [30], functional impairment [30, 31], disability and diminished quality of life [16, 30, 31], disability, pain and fear for the future [16].

Treatment

Majority of the patients with vertebral fractures are treated conservatively. The mainstay of treatment is to reduce pain and improve mobility [16]. Secondly, it is accompanied by the treatment of the osteoporosis. Teriparatide together with calcium and vitamin D has been shown to reduce severe and multiple fractures by approximately 85% [32]. Pain is usually treated with analgesics, the NSAIDs, and in severe cases opiates and calcitonin may be considered. In some patients in the acute or in the chronic phase, vertebral augmentation is considered through either vertebroplasty or kyphoplasty [33]. They are minimally invasive and aimed at pain control [34]. There is often immediate and marked pain relief in 70–95% of patients with vertebroplasty [35]. Kyphoplasty has the benefit of kyphosis reduction and less cement leakage [36]. Kyphoplasty has also been shown to reduce pain and restore vertebral body height [34, 36]. Fracture reduction is best achieved in acute fractures [36].

Sacral Insufficiency Fractures

Introduction

Sacral insufficiency fracture is a subtype of stress fractures [37]. The exact incidence of sacral insufficiency fractures is not known largely because of the lack of awareness resulting in their being undiagnosed [38]. Majority of the fractures occur in the elderly females [39] and are frequently bilateral [40]. It usually occurs in osteoporotic bone, metabolic bone disease and following radiotherapy [41].

Clinical Manifestations

Majority of the patients present with low back pain or pelvic pain following a history of trauma, minimal or unremembered [38]. Sacral insufficiency fractures are often mistaken both clinically and radiologically with metastatic disease [41, 42].

Diagnosis

It is often overlooked in elderly patients with pelvic pain with minimal trauma [38, 43]. Plain X-ray in general is normal, and computed tomography is useful to make a diagnosis and exclude such conditions as metastatic bone disease, spinal stenosis and sacroiliac joint infection [38, 40]. Bone scintigraphy in the detection of sacral fractures is well

accepted [39, 44]. Most frequently there is increased uptake in the body of the sacrum, and both sacral alae give rose to an H- or butterfly-shaped appearance, but this sign is often not seen [39] (Fig. 1). To establish the diagnosis, CT and MRI scans are preferred examinations [39].

Treatment

The mainstay of treatment is bed rest, analgesics and treatment of the underlying osteoporosis. Patients who are refractory to conservative treatments should be considered for vertebroplasty (sacroplasty) or kyphoplasty [45].

Impact

After the age of 50 years, 13% of white men and about 40% of white women will have at least one fragility fracture [46]. The incidence of hip fractures rises exponentially with increase in age irrespective of gender and ethnicity [7]. The mean age of people sustaining hip fractures is 75–80 years [47, 48]. In the elderly, QoL is dependent on co-morbidity, mobility and ability to perform activities of daily living and fracture complaints [49]. About 40% are unable to walk 1 year after hip fracture, 60% have difficulty in performing at least one essential activity of daily living [46], and about 19–27% are institutionalised for the first time [46, 50] The inability to walk results in loss of independence. Excess deaths after hip fracture amount to 12–20% [50]. Mortality rate is highest in men over the age of 75 years [46]. Fractures have become a public health problem in terms of costs, morbidity and mortality [51] in almost every nation; demographic and epidemiological trends suggest that hip fractures will be a major health problem [52] in the near future with significant costs. In the United States, quarter of a million hip fractures annually cost over 8 billion dollars [50], and in Australia the direct costs associated with these fractures amount to an estimated $1.9 billion each year [53]. About 10% of postmenopausal women with vertebral fractures have chronic pain that interferes with their daily functioning and affects quality of life [50]. Fragility fractures are associated with considerable pain and even death for the affected patients [54] (Boxes 1, 2 and 3).

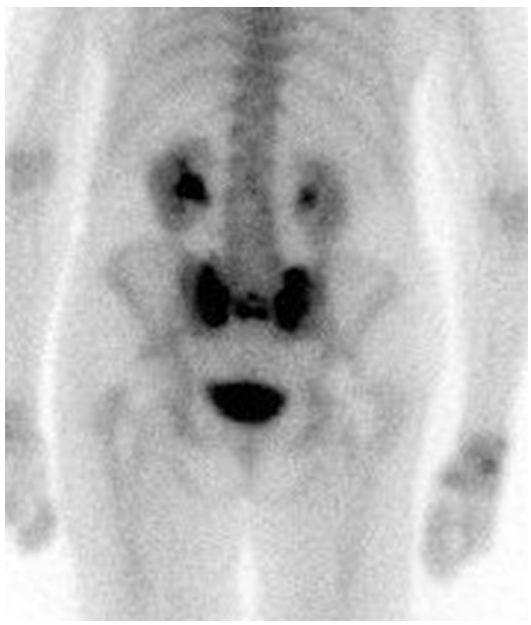

Fig. 1 Bone scan showing classical 'Honda sign' in sacral insufficiency fractures. Referenced with permission from Dr. Leo Ha

Box 1 Key Points. Hip Fractures

The incidence of hip fractures rises exponentially with increase in age irrespective of gender and ethnicity.

There is very little trabecular bone in the femoral neck and the blood supply is poor [11]. In contrast there is large amount of trabecular bone in the intertrochanteric region with good blood supply [11].

The two groups differ in many ways, the incidence, mechanism of injury, mortality, treatment and complications.

Apart from age, gender and ethnicity, there are a number of determinants that may influence the outcome which can provide prognostic information.

(*continued*)

Box 1 Key Points. Hip Fractures (continued)

Cardiac involvement has been reported as the main risk index of postoperative complications and death.

There is a high prevalence of preoperative medical problems in this group of patients.

The extent of the evaluation will depend on the status of the patient and the urgency for intervention.

Postoperatively there is increase in occurrence of deep vein thrombosis, delirium, persistent pain, urinary tract and wound infections and pressure ulcers.

Box 2 Key Points. Vertebral Fractures

Considering all osteoporotic fractures, 46% of the fractures are vertebrals, 16% hip and 10% the wrists [15].

The incidence of vertebral fractures increases with age in both men and women, and in both the common type of fracture was the wedge-shaped fracture.

One in five patients with incident vertebral fracture will experience a further vertebral fracture within a year [16, 30].

Acute pain is the commonest form of presentation.

Other symptoms include postural changes and loss of height including kyphosis [30].

Majority of the patients with vertebral fractures are treated conservatively.

The mainstay of treatment is to reduce pain and improve mobility and treatment of the osteoporosis [16]. Kyphoplasty has also been shown to reduce pain and restore vertebral body height [34, 36].

Box 3 Key Points. Sacral Insufficiency Fractures

Sacral insufficiency fracture is a subtype of stress fractures [37].

Box 3 Key Points. Sacral Insufficiency Fractures (continued)

It usually occurs in osteoporotic bone, metabolic bone disease and following radiotherapy [41].

Patients present with low back pain or pelvic pain following a history of trauma, minimal or unremembered [38, 40].

The mainstay of treatment is bed rest, analgesics and treatment of the underlying osteoporosis.

Multiple Choice Questions

1. The following are true of hip fractures EXCEPT:
   A. The mean age of people sustaining hip fractures is 60–70 years.
   B. Cardiac involvement has been reported as the main risk index of postoperative complications and death.
   C. There is a high prevalence of preoperative medical problems in this group of patients.
   D. The extent of the evaluation will depend on the status of the patient and the urgency for intervention.
2. The following are true of osteoporotic vertebral fractures EXCEPT:
   A. The identification of vertebral fractures can be controversial.
   B. One in two patients will experience another vertebral fracture within a year.
   C. The bone loss in the vertebrae is mainly trabecular.
   D. There is often immediate and marked pain relief in 70–90% of patients with vertebroplasty.
3. The following are true of sacral insufficiency fractures, EXCEPT:
   A. They usually occur in osteoporotic bone with little or no trauma.
   B. The ‘H’ sign on scintigraphy is diagnostic and this sign is always present.
   C. It is often confused with metastatic bone disease or sacroiliac joint infection.
   D. Plain X-ray is sufficient to make a firm diagnosis.

MCQ Answers

1=A; 2=B; 3=D

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Part IX

Endocrine Disorders in the Elderly

Aging strongly affects the entire endocrine system. Worldwide the incidence and prevalence of diabetes mellitus increases with age. With the adoption of the new diagnostic criteria and people living longer, the prevalence of DM is likely to increase. A new problem that is disturbing is the rise of type 2 diabetes mellitus (T_2DM) in young people. Part IX provides an update on the mechanisms of action, use, contraindications, and adverse effects of the medications used in the clinical management in DM. Thyroid abnormalities are relatively common in the general population but have important clinical implications in the elderly because of the coexisting comorbidities and increased risk of heart disease and hypercholesterolemia. The diagnosis of thyroid disease in the elderly can be problematical. The incidental finding of asymptomatic PHPT in the older patient poses problems and there is little guidance on how to manage them. The present review will highlight and provide information on issues that are common to the elderly.

Diabetes Mellitus in the Elderly

47

Contents

Abstract

Worldwide the incidence and prevalence of diabetes mellitus (DM) increase with age. With the adoption of the new diagnostic criteria and people living longer, the prevalence of DM is likely to increase. A new problem that is disturbing is the rise of type 2 diabetes mellitus (T_2DM) in young people. This chapter provides an update on the mechanisms of action, use, contraindications and adverse effects of the medications used in the clinical management in DM. The elderly often do not present with usual classic symptoms of polyuria, polydipsia and polyphagia. They may present only with one or more of the geriatric syndromes, namely, falls, incontinence, decreased cognition or fatigue, lethargy or weight loss. The management of diabetes in the elderly is complex, but in general the principles of management are similar to that of younger patients.

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_49

Keywords
Diabetes mellitus · Type 2 diabetes mellitus (T_2DM) · Prevalence of DM · Diabetic ketoacidosis (DKA) · Hyperosmolar hyperglycaemic state (HHS)

Introduction

Ageing strongly affects the entire endocrine system [1, 2]. There is a progressive decline in glucose tolerance which occurs from the third decade through to the ninth decade [3]. Worldwide the incidence and prevalence of diabetes mellitus increase with age, and during the past two decades, the incidence and prevalence have increased enormously in the United States [4]. In the industrial countries, the greatest increases in the total number of cases of diabetes are among the elderly people [5]. This is not only due to the increase in the ageing population, but there is an absolute increase in the prevalence of DM in the elderly people [6]. It affects about 40% of the elderly over the age of 80 years [7], but there is a decline in the very old [8]. A new problem that is disturbing is the rise of type 2 diabetes mellitus (T_2DM) in young people [9, 10]. The young-onset T_2DM is more aggressive than T_1MD to develop complications such as ischaemic heart disease and neuropathy [11]. Immune-mediated diabetes commonly occurs in childhood and adolescence but can occur in the eighth or ninth decades of life [12]. Although nearly 20% of aged more than 65 years are affected, nearly half of them are undiagnosed [13]. The elderly with diabetes are a heterogenous group [14] and include patients living in the community or in aged care facilities [4]. The elderly with type 2 diabetes have an increased prevalence of comorbidities [15, 16] but underrated, and complications include geriatric syndromes such as cognitive disorders [17, 18], physical disability, falls, fractures and frailty [15, 19, 20]. The epidemiology of diabetes in the elderly is not well understood. With the adoption of the new diagnostic criteria and people living longer, the prevalence of DM is likely to increase.

It is a disorder of multiple causes. The demonstration of microvascular and macrovascular complications at lower levels of glucose concentrations has led to new recommendations by the World Health Organization [21] and the American Diabetic Association [12]. Type 1 (due to beta-cell destruction usually leading to absolute insulin deficiency)-auto-immune or idiopathic. Around the time of diagnosis, it is associated with islet cell antibodies and HLA DR3 and DR4 [22]. The term 'type 1a' is given to the development of type 1 diabetes in adulthood [22]. Type 2 may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance. Other specific types are genetic defects of beta-cell function; genetic defects in insulin action; diseases of exocrine pancreas: pancreatitis, trauma, pancreatectomy, haemochromatosis and neoplasm; endocrinopathies: Cushing's, acromegaly, hyperthyroidism, phaeochromocytoma and others; and gestational diabetes mellitus among others [12, 21].

The American Diabetes Association and World Health Organization diagnostic criteria are as follows [21]:

Fasting plasma glucose >7.0 mmol/L

Fasting whole blood glucose level >6.1 mmol/L

A 2-h post-glucose load plasma glucose >11.1 mmol/L

A random

* Prediabetic stage – fasting plasma glucose 5.6–7.0 mmol/L; evidence supports lifestyle interventions to prevent or delay onset of diabetes. The detection of diabetes by measuring the plasma glucose levels is heightened in the young. In the elderly however, about 31% may be missed [23, 24]. A 2-h post-glucose test may be useful in detecting diabetes in the elderly if there is any clinical uncertainty [25].

Type 1 diabetes may be due to an auto-immune destruction of the beta cells or idiopathic. Multiple genes and environmental factors play an important role in type 2 diabetes and contribute to the development of insulin resistance in the liver and muscle as well as to beta-cell failure [26, 27]. Environmental risk factors include those that are modifiable such as obesity and physical activity and non-modifiable such as genetic factors, older age, race/ethnicity and positive family

history. It is important to know that both type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes occur in the elderly [25].

Clinical Presentation

In the elderly, presentation is different. The renal threshold for glucose increases, and glucosuria does not occur at usual levels. There is decreased thirst as age advances, and polydipsia is not usually seen. Dehydration occurs due to the altered thirst and delayed supplementation of fluid [25]. The elderly often do not present with usual classic symptoms of polyuria, polydipsia and polyphagia. They may present only with one or more of the geriatric syndromes, namely, falls, incontinence, decreased cognition or fatigue, lethargy or weight loss [27]. Diabetics are prone to-infections especially recurrent urinary tract infection. They may present with one of the complications of diabetes including neurological symptoms such as paresthesiae, pain, muscle weakness isolated nerve palsies or autonomic dysfunction as postural hypotension and incontinence. Ketoacidosis seldom occurs spontaneously but is associated with stress of another illness such as infection.

Management of Diabetes in the Elderly

The management of diabetes in the elderly is complex, but in general the principles of management are similar to that of younger patients [28, 29]. The evaluation and treatment should be individualized [30] and multi-faceted, and a multidisciplinary approach will provide the most beneficial outcome. The goals of treatment should be conservative.

Nutrition, Physical Activity and Education

Lifestyle changes can be more productive than drug therapy [30, 31]. Nutritional and physical activities are the main initial strategies in the management of diabetes at all ages. A low-fat diet and exercise can reduce insulin resistance and are associated with mild weight loss [32, 33]. Although aerobic or resistance exercises are recommended, the exercise prescribed need not be intense to render benefit [34]. Apart from education with regard to diet and exercise, efforts must be made to improve self-managing skills. The risk factors affecting progression are shown in Box 1.

Box 1 Risk Factors Affecting Progression

Poor glycaemic control
- Poor blood pressure control
- Cigarette smoking
- Hyperlipidaemia
- Urinary albumin excretion
- Genetics
- Ethnicity

Pharmacological Treatment

Patients who do not attain expected glycaemic control on individualized exercise and diet programme will require pharmacological therapy. Age-related changes to drug metabolism increase the risk of adverse effects [29]. The changes in pharmacokinetics will require appropriate precautions when prescribing for the elderly diabetic. Drug-drug interactions, for instance, the action of sulphonylurea, may be potentiated by such medications as non-steroidal anti-inflammatory drugs and clofibrate and cause hypogylcaemia. The elderly diabetic is susceptible to hypoglycaemia. Some of the factors that predispose them to hypoglycaemia are changes in memory and cognition [28, 35]; geriatric syndromes such as depression, falls, urinary incontinence [20] together with isolation and dependence; non-compliance with medications; erratic nutritional intake [35]; the presence of cardiac, hepatic and renal disease; and other comorbid conditions. The pharmacological agents used in the treatment of diabetes are classified as follows (Box 2).

Box 2 Antidiabetic Agents

1. Insulin secretagogues
   A. Sulphonylureas
      First generation: tolbutamide and chlorpropamide
      Second generation: glibenclamide, glipizide, gliclazide and glimepiride
   B. Meglitinides: repaglinide and nateglinide
2. Insulin sensitizers
   i. Biguanides: metformin and phenformin
   ii. Thiazolidinediones: rosiglitazone, pioglitazone and rivaglitazone
3. Alpha-glucoside inhibitors: acarbose and miglitol
4. Incretins
   Dipeptidyl peptidase-4 (DPP-4) inhibitors: sitagliptin, saxagliptin and vildagliptin
5. Glucagon-like peptide-1 (GLP-1): exenatide, liraglutide and pramlintide
6. Insulin

Mechanism of Action, Use, Contraindications and Adverse Effects

The sulphonylureas enhance the first phase of insulin secretion as well as the second phase of insulin release [36]. They are used when metformin is contraindicated. Contraindication to their use is severe renal insufficiency. Side effects include weight gain and a greater risk of hypoglycaemia [28, 37]. First-generation sulphonylureas such as chlorpropamide should be avoided in the elderly because of their long life [24]. The incidence of hypoglycaemia however is low with the shorter-acting agents [38].

The meglitinides – repaglinide and nateglinide – are unrelated to the sulphonylureas; both promote secretion of insulin from pancreatic beta cells act by rapidly activating post-prandial insulin release. The short life of these drugs enhances the first phase of insulin release, but the effect of the second phase is not prolonged [39]. All insulin secretagogues should be avoided in patients with liver disease and used with caution in patients with renal dysfunction [24].

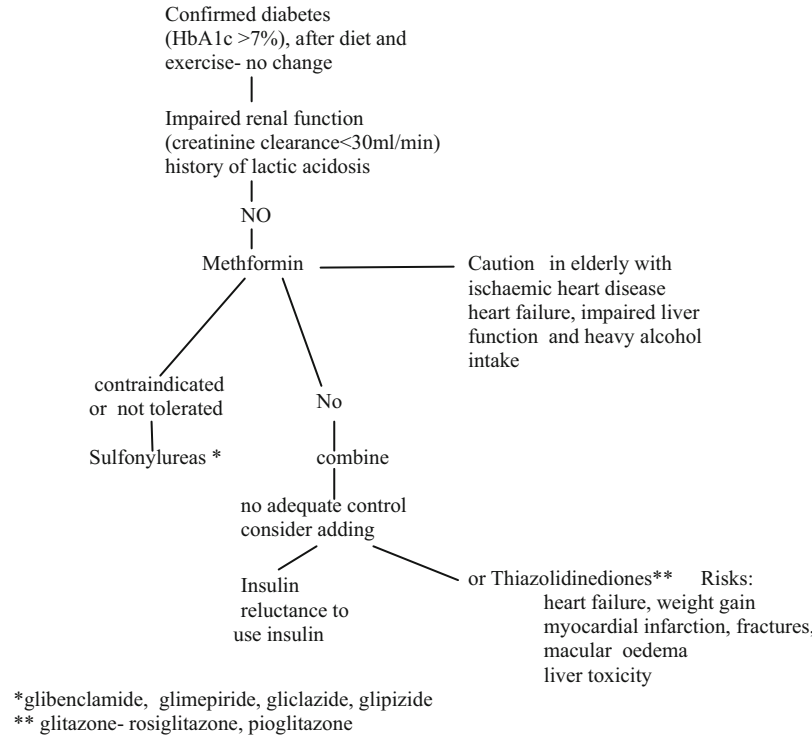
In biguanides, the precise mechanism of action is unclear [40]. Its antihyperglycaemic properties are attributed to increase in the peripheral tissue insulin sensitivity and to suppression of hepatic glucose production [41]. Improved sensitivity is due to an action mediated through the post-receptor signalling pathways for insulin [42]. It can be used to initiate treatment in the elderly [30] and has beneficial effects on several cardiovascular risk factors and does not cause weight gain [31]. It is contraindicated in impaired renal function in the elderly (should not be given if the creatinine clearance is <60 mg/dl) [24], ischaemic heart disease, heavy alcohol consumption and lactic acidosis. Side effects include increase risk of gastrointestinal effects [28], anorexia and weight loss in the elderly [43].

The thiazolidinediones enhance insulin effects by activating the peroxisome proliferator-activator receptor (PPAR) gamma that regulates expression of specific genes especially in fat cells interfering with the expression and release of insulin mediators of insulin resistance in the adipose tissue [44]. Rosiglitazone has been shown to be effective and safe in the elderly [45]. They can be used alone or in combination. Contraindications include ischaemic heart disease, liver disease and heart failure [24]. Side effects are an increase risk of myocardial infarction, increase risk of fracture, macular oedema and liver toxicity.

The alpha-glucosidase inhibitors inhibit the intestinal alpha-glucosidase enzyme by retarding the rate of carbohydrate digestion [46]. They are used in mild diabetes [24] when others are not tolerated and do not cause hypoglycaemia. They are contraindicated in chronic GI inflammatory disease and severe renal insufficiency. Side effects are adverse effects on liver function in high doses.

Incretins are a group of intestinal peptides that enhance insulin secretion after ingestion of food [28]. The two main incretins are (i) inhibitors of glucagon-like peptide-1 (GLP-1) degrading enzyme dipeptidyl peptidase-4 (DPP-4) and improving diabetic control through incretin hormone-mediated increase in both alpha- and

Algorithm 1 Pharmacological treatment of diabetes mellitus in the elderly



Information source: National Prescribing Service Newsletter 56, [53].

beta-cell responses to glucose [47]. They are effective, can be used alone or in combination with lower incidence of hypoglycaemia, without weight gain [48, 49], and are well tolerated [50]. The adverse effects of DPP-4 inhibitors are nasopharyngitis and/or upper respiratory tract infections [28]. (ii) Glucagon-like peptide-1 (GLP-1) suppresses the glucagon secretion [51]. Pramlintide is a synthetic analogue of amylin [30].

Insulin is used when oral agents fail and used as monotherapy or in combination.

(i) Long-acting insulin glargine (Lantus) no peak/duration 24 h; insulin detemir (Levemir) peak 9 h/duration 12–20 h. Used for people with symptom or nocturnal hypoglycaemia when on isophane. Long-term safety, no information risk of severe hypoglycaemia
(ii) Fast-acting insulin aspart, insulin glulisine
(iii) Isophane peak 4–6 h/duration 16–24 h

The long-acting insulin analogues glargine and detemir have only slight clinical advantages over NPH (neutral protamine Hagedorn) [52] and higher costs. NPH is the preferred first-line insulin for treatment of type 2 diabetes [52].

An Algorithm 1 is provided that summarizes the steps involved in the pharmacological treatment of diabetes in the elderly.

Management and Treatment of Complications of Diabetes

Acute complications are medical emergencies:

i. Diabetic ketoacidosis (DKA)
ii. Hyperosmolar hyperglycaemic state (HHS)

DKA and HHS are the two most serious acute complications of diabetes mellitus due to various degrees of insulin deficiency and elevations of counter regulatory hormones. DKA is characterized by hyperglycaemia and ketoacidosis [54], and the precipitating cause is either infection or insulin omission. HHS is

Table 1 Distinguishing features, DKA and HHS

	DKA	HHS
Precipitating cause	Infection	Undiagnosed DM
	Insulin omission	Infection and substance abuse
Manifestations	Hyperglycaemia	Hyperglycaemia
	Ketoacidosis	Diuresis
		Dehydration
Cornerstone of therapy[a]	Insulin	Fluid replacement
Prognosis in >65 years	Worsened in the presence of coma and hypotension	Worsened in the presence of coma and hypotension
Mortality	3–5%	15%

Information sources: [57–59]
[a]Three-pronged approach fluid administration, intravenous insulin infusion and electrolyte replacement

characterized by hyperglycaemia, osmotic diuresis, dehydration [55] and little or no ketosis [56], and precipitating causes are undiagnosed diabetes, infection and substance abuse (Table 1).

Management of Diabetic Ketoacidosis

I. Use isotonic salines, 1 L in 15 min, the second litre over 1 h and the third litre over 2–3 h depending on the response.
II. Insulin therapy. Administer regular insulin three to five units IV or ten units IM or infusion pump (10 units of insulin and then 50 units regular insulin to 50 ml of saline in pump). Another three to five units may be needed 1 h after the first dose, depending on the glucose level. The aim is to reduce the blood sugar level by half in about 12 h.
    I. Avoid potassium until serum K+ result is available and do not give it if the serum K + is >5.5 mmol/L.
    II. Bicarbonate infusion in severe acidosis, i.e. pH <7.0 (H+ concentration >100 nmol/l).
    III. Dextrose is used to correct intracellular depletion and if the blood sugar is <15 mmol/l.
    IV. Plasma expander given if the blood pressure does not improve rapidly; monitor urine output and central venous pressure.

Management of Hyperosmolar Hyperglycaemic State

It is requisite that the hyperglycaemic hyperosmolarity is corrected rapidly by volume replacement with solutions that have tonicity pertinent to the level of the hyperosmolarity [57]. The rate of replacement will be regulated by the hypovolaemia as well as by the renal and cardiac function [57]. Significant hyperosmolarity prevails if the effective osmolarity is above 320 mOsm per L and is a guide as to the tonicity of the replacement solution [58, 59]. Osmolarity can be calculated as follows: Plasma osmolarity $= 2(\text{Nammol}/l) + K\ \text{MMol}/l) = \text{ureammol}/l + \text{glucose}\ \text{mmol}/l$. Multielectrolyte solutions such as lactated Ringer's solution are preferred to normal saline solution [57]. Insulin is also administered. Cerebral oedema is rare in adult patients with hyperosmolar hyperglycaemic syndrome [58]. Provided the serum potassium level is below 5 mEq per L (5 mmol per l) and the electrocardiogram shows no evidence of hyperkalaemia, potassium replacement should begin in the first hour [57].

Chronic Complications of Diabetes

Long-standing diabetes is associated with damage and dysfunction of large (macrovascular) and small (microvascular) blood vessels resulting in damage to the various organs.

Pathological changes in the microvasculature with capillary basement thickening and endothelial hypoperfusion result in diminished oxygen and hypoxia. Microvascular dysfunction occurs early in diabetes and parallels the progression of neural dysfunction [60]. Risk factors are shown in Box 3.

Box 3 Risk Factors for Complications
Duration of diabetes
- Poor blood sugar control
- Poor blood pressure control
- Presence of kidney disease
- Smoking
- High cholesterol

Macrovascular

The macrovascular complications associated with diabetes include cardiovascular, cerebrovascular and peripheral arterial disease. The most common cause of death for elderly patients with diabetes is ischaemic heart disease. The risk of coronary artery disease is increased in patients with poor glycaemic control. There are several mechanisms that contribute to the increased risk of coronary artery disease in diabetics, namely, hypertension, hyperglycaemia, hyperlipidaemia and lifestyle factors (smoking, diet). Other factors that maycontribute are oxidative stress, impaired fibrinolysis, endothelial dysfunction, hypercoagulability, glucose toxicity and platelet hyperaggregability [61, 62]. Diabetes and stroke together are a major cause for mortality and morbidity worldwide. It is estimated that the risk of stroke is increased by 1.5- to threefold for patients with diabetes [63, 64]. Diabetes also doubles the risk of stroke recurrence [65] and with poor outcome. The risk of development of peripheral arterial disease increases threefold to fourfold in patients with diabetes [66]. Aggressive management and treatment of the risk factors are crucial.

Microvascular

Microvascular complications include nephropathy, neuropathy and retinopathy. Microvascular complications can develop at least 7 years before the clinical diagnosis of type 2 diabetes [67].

Diabetic Nephropathy

Diabetic nephropathy is a clinical syndrome characterized by persistent albuminuria, hypertension and renal insufficiency. It is the leading cause of chronic renal failure in the United States and Western countries and accounts for 40% of new cases of end-stage renal disease (ESRD) in the United States [68]. Histological changes are seen in the glomerulus and the renal vasculature. Nodular sclerosis occurs in the mesangial compartment of the glomerulus (known as the Kimmelstiel-Wilson nodules/lesion). In the established nephropathy, there is diffuse glomerular sclerosis. In addition, there is glomerular membrane thickening. Abnormalities in the tubulo-interstitium include chronic interstitial inflammation and a predisposition to papillary necrosis [69].

Management of Nephropathy

Patients 55 years or older who were randomized to ramipril 10 mg/day or placebo in the MICRO-HOPE [70] study showed a 24% reduction in the overt development of nephropathy in the treatment group. The ACE inhibitors may in part have the ability to lower glomerular capillary pressure and thereby exert a vascular protective and reno-protective effect [71]. The primary end point of the RENAAL (Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan) [72] study was the time of the first occurrence of doubling of serum creatinine, ESRD or death. The patients with type 2 diabetes, proteinuria and elevated creatinine were given either losartan 50–100 mg daily or placebo. The study was ended 13 months ahead of schedule. The losartan group demonstrated a 25% reduction of a doubling of the serum creatinine

concentration, 28% risk reduction of ESRD and 35% decrease in the level proteinuria.

Management guidelines are summarized in Box 4.

Box 4 Management Guidelines of Diabetes

1. Test for microalbumin.
   At time of diagnosis of type 2
   After 5 years in type 1
   Subsequent examination
   Performed annually
   Normal urine albumin excretion is less than 30 mg/24 h.
   Microalbumin 30–299 mg/24 h.
   Macroalbumin >300 mg/24 h (ADA 2004 [12]).
2. Lifestyle changes.
3. Glycaemic control.
4. Blood pressure control.
5. Drug therapy – ACE inhibitors and ARBs can reduce microalbuminuria and may retard progression to overt diabetic nephropathy.

Information source: ADA 2004 [12]

Diabetic Neuropathy

The prevalence of diabetic neuropathy varied from 28.5% [73] up to 50–60% [74, 75]. About one in five patients with diabetes is afflicted with neuropathy which is the most common complication of diabetes. It can occur in both type 1 and type 2 diabetes. Peripheral neuropathy is common in elderly patients with type 2 diabetes mellitus. Patients with diabetes develop neuropathy at any time, but the risk increases with age and duration of the diabetes. In type 1 diabetics, distal polyneuropathy becomes symptomatic after many years of chronic prolonged hyperglycaemia whereas in type 2 after a few years and known poor glycaemic control. A cross-sectional study of 6,487 patients found a 28.5% prevalence of neuropathy, 8% had neuropathy at the time of diagnosis of diabetes mellitus and 50% after 25 years [73].

Clinical Manifestations

Diabetic neuropathy has been classified into four types, namely, peripheral, autonomic, proximal and focal. Sensory, motor or autonomic functions are affected in varying degrees with sensory abnormalities predominating. Thomas [76] separated them into rapidly reversible or more persistent. The former included minor sensory symptoms, and nerve hypoxia likely causes for their origin. The latter includes distal symmetric polyneuropathy, distal axonopathy and focal or multifocal lesions giving rise to cranial and limb neuropathies [76]. They have been classified as acute sensory and chronic sensori-motor, with complete recovery within a year in the former and in the latter symptoms may persist for years [77].

Peripheral (Symmetrical Distal Sensori-motor) Neuropathy

Distal sensory and sensori-motor polyneuropathy is insidious in onset. The longer nerve fibres are affected early and to a greater degree than the shorter because nerve conduction velocity is slowed in proportion to the nerve's length. Thus the earliest symptoms typically involved the toes and then ascend. Symptoms include numbness of the extremities, tingling, burning sensation with sharp pains or cramps worse at night [78]. The feelings of numbness may be likened to wearing socks or gloves. In addition there may be loss of balance and coordination and hypersensitivity to touch [79]. Motor symptoms may include weakness, and in the upper extremities, there may be impaired fine hand coordination. Foot slapping or frequent tripping may be early symptoms of foot weakness.

Painful neuropathy is a distal symmetrical neuropathy, less common and seen in about 4–7% of diabetics involving predominantly the small diameter sensory fibres (A delta and C fibres). Painful paresthesiae such as burning, lancinating, stabbing and cramps are worse at night together with a feeling of tightness and/or pressure around their feet, tingling, vibration, allodynia and hyperalgia. There is loss of pain and temperature with

Table 2 Cause and treatment of diabetic painful neuropathy

Symptom	Cause	Treatment	Side effects and other
Painful neuropathy	Involvement of small diameter sensory fibres (A delta and C fibres)	1. Tight glycaemic control	
		2. TCAs[a]	Cardiac toxicity, fatal, arrhythmias, blurred vision, dry mouth, postural, hypotension, urinary, retention and constipation
		3. SSRI[b]	Less effective than
TCAs		4. Anticonvulsants[c]	Drowsiness, dizziness, ataxia, diplopia and nystagmus
			Gabapentin no significant
			Difference in pain relief vs amitriptyline
		5. Capsaicin cream	
		6. Analgesics[d]	
		7. Other[e]	

Information sources: Zeigler et al. [75] and Bril et al. [85]
[a]TCAs – imipramine, amitriptyline, nortriptyline and desipramine
[b]SSRIs – fluoxetine, paroxetine, sertraline and citalopram
[c]Anticonvulsants – gabapentin, pregabalin compares favourably with amitriptyline; carbamazepine, oxcarbazepine, effective but unsafe for diabetic neuropathy
[d]Analgesics – opioid analgesics such as codeine or oxycodone can cause serious side effects and addiction. Oyycodone 10 mg to a maximum of 100mg/day
[e]Other – acupuncture and alpha-lipoic acid an antioxidant daily oral dose 600–1,800 mg [76]

relative sparing of proprioception and distal reflexes. Diabetic neuropathic cachexia a syndrome characterized by painful peripheral neuropathy, depression, weight loss and anorexia occurs especially in men and usually resolves within a few months without treatment [78]. The cause and treatment of painful neuropathy are shown in Table 2.

Autonomic Neuropathy

In one series the prevalence of diabetic autonomic dysfunction was 70% and the prevalence of definite neuropathy was 40% [80]. The prevalence in randomly selected asymptomatic diabetic individuals was about 20% [81] and incidence 20–50% [82]. The majority of patients with diabetic autonomic neuropathy have symptoms that are mild, a few are with florid features and hence the prevalence may be greater than what was suspected [83]. It is more likely to occur in people who have had poorly controlled diabetes over many years. It can affect all systems and predominantly affects the cardiovascular, gastrointestinal and genitourinary systems. It affects the blood pressure and heart rate and may cause sharp drops in blood pressure on change of posture (postural hypotension). Gastrointestinal symptoms include belching, abdominal pain, constipation or uncontrolled diarrhoea or both and delayed gastric emptying (gastroparesis) [79, 84]. Incomplete emptying of the bladder with urinary incontinence and frequent urinary tract infections together with erectile dysfunction and retrograde ejaculation and increased or decreased sweating and oedema are seen in autonomic neuropathy [79, 84] (Table 3).

Proximal Neuropathy

Proximal neuropathy is also called diabetic amyotrophy or femoral neuropathy. This is characterized by weakness and wasting of the thigh muscles with difficulty to rise from a seated position. The patients are usually older than 50 years with poorly controlled diabetes. It often starts acutely and unilaterally with severe pain in the thigh, hip and buttock [79]. There is

Table 3 Autonomic neuropathy

Gastrointestinal		
Diarrhoea		Codeine phosphate
		Dietary change
Gastroparesis		Metoclopramide
		Domperidone
		Smaller, more
		Frequent meals
Cardiovascular		
Postural hypotension	Fall of systolic pressure on standing (>30 mmHg)	Simple lifestyle
		Measures; compression
		Stockings; fludrocortisone
Genitourinary		
Bladder dysfunction	Incomplete emptying	Behavioural techniques; treat infection
Sexual dysfunction		Medications in some; sildenafil, tadalafil
Male		Vacuum devices
		Penile implant
Female		Vaginal lubricants
		Oestrogens

Information sources: Vinik et al. [81], Clarke et al. [83] and Ewing et al. [84]

accompanying weight loss in more than half the patients. Numbness and paresthesiae may occur. It may be treatable with immunotherapy.

Focal Neuropathy

Occasionally diabetic neuropathy involves specific nerves in the head trunk and leg and may cause severe pain. In cranial mononeuropathy, the cranial nerves usually involved are the III, IV, VI, VII and II. In somatic mononeuropathy, it is compression or entrapment – carpal tunnel syndrome [79]. In polyradiculopathy, the involvement of the intervertebral nerves gives rise to numbness in a dermatomal distribution and commonly occurs in older patients and accompanied by weight loss.

Management of Neuropathy

Good glycaemic control remains the mainstay of treatment of diabetic neuropathy which includes maintenance of healthy lifestyle-physical activity, weight reduction, smoke cessation, avoidance of alcohol, healthy eating plan and blood pressure under control. Distressing painful symptoms, foot ulceration in some, leading to amputation and debilitating symptomatic autonomic symptoms are inherent adversities for the patient with diabetic neuropathy. Medications used which have demonstrated efficacy in randomized, controlled trials include the tricyclics, SSRIs, anticonvulsant, antiarrhythmics and opioids [77]. Pregabalin has been validated to be effective in treating painful neuropathy [85]. Others such as duloxetine, venlafaxine, gabapentin, valproate opioids and capsaicin are probably effective [85]. The process is generally progressive, and treatment at present is limited to alleviation of pain and associated symptoms. Injury to foot due to sensory loss may lead to infection, ulceration and which may require amputation.

Diabetic Retinopathy

Diabetic retinopathy (DR) is the most common chronic microvascular complication of diabetes and is due to progressive damage to the vessels in the retina and caused by sustained hyperglycaemia. The overall prevalence of DR however varies across different populations [86]. It occurs in both type 1 and type 2 diabetes. DR is basically

a manifestation of small vessel disease and is a function of the metabolic defect rather than the type of diabetes [87]. Its prevalence increases with the duration of the disease and with age. It is also related to the blood pressure and glycaemic control, and there is ample evidence that the effects of diabetes on the retina can be delayed or even curtailed by rigorous control of the blood sugar level [88]. There are two grades of retinopathy in diabetes mellitus clinically, background and proliferative [87]. Background retinopathy is manifested by focal closure of retinal capillaries, microaneurysms and associated punctuate haemorrhages, serous exudates and, occasionally cotton-wool spots secondary to acute ischaemia. These changes rarely cause serious visual problems [87]. On the other hand proliferative retinopathy is more threatening and involves the growth of new blood vessels in front of the retina where they tend to bleed and through concomitant fibroblastic activity, tear and retinal detachment. The common symptoms are shown in Box 5. The complications are vitreous haemorrhage, retinal detachment, glaucoma and blindness.

Box 5 Common Symptoms in Diabetic Retinopathy

No symptoms at first
- Mild visual problems
- Blurred or disturbed vision
- Floating bodies or blind spots
- Increased sensitivity to glare
- Difficulty seeing at night
- Visual loss

Management and Treatment

1. Comprehensive eye examination by ophthalmologist or optometrist – type 1, within 3–5 years after onset of diabetes; type 2, shortly after diagnosis [89]
2. Subsequent examinations – annually or more frequently if retinopathy is progressing
3. Prompt care of ophthalmologist – patients with macular oedema, severe NPDR or any PDR
4. Early referral to an ophthalmologist for patients with type 2 diabetes with severe NPDR
5. Visual rehabilitation for patients with visual loss

Impact

Diabetes in the elderly poses special problems; not only are there the risk of established macrovascular and microvascular complications but a high degree of comorbidities and the age-related risk of developing or worsening of many geriatric syndromes such as cognitive impairment, chronic pain, falls, polypharmacy, urinary incontinence and depression [8, 9]. The end result will have a direct impact on the quality of life, the extent of independence and the demand on caregivers [6]. The macrovascular and microvascular complications are well recognized, but some of the complications associated with the elderly which include cognitive disorders, physical disabilities, falls, fractures and other geriatric syndromes are not often fully realized and addressed. In elderly patients, diabetes mellitus increases the risk for development or worsening of the many common geriatric syndromes. Several studies have shown an association between diabetes and cognitive decline [17, 18] and a strong association with stroke-mediated dementia [17, 90]. There is an increased risk of falls and hip fractures in diabetic women compared to nondiabetic women [19, 91]. They are equally important for the efficient treatment of elderly diabetic patients. These symptoms are sometimes present before the diagnosis is made but inevitably emerge as the disease progresses. They are disabling and can reduce the quality of life, increase caregiver burden and shorten life expectancy. The elderly are a heterogenous group [28–31] linked to multiple and varied comorbidities [28, 29, 35], broad difference in functional status, bound to disability and frailty [28], limited life expectancy, numerous medications with adverse effect to drugs [30] and higher risk of severe hypoglycaemia [29, 31, 35]; the goals of treatment should be conservative.

There are a high incidence and prevalence of functional difficulties and a heavy load of comorbidity [92]. It has been shown that elderly patients with type 2 diabetes have excess of cognitive dysfunction associated with disabilities relating to diabetes self-care and greater dependency [93] triggering loss of autonomy, impact on quality of life and demands on caregivers [6]. The elderly DM is at higher risk of developing disabilities related to mobility and daily tasks [6]. The burden of complications, visual changes, kidney failure, alterations in cardiac function and peripheral vascular disease will have a significant impact on the functional status [94], quality of life and substantial healthcare costs [95]. In the United States, the estimated cost of diabetes in 2007 was about 174 billion dollars, and the average per person's annual out-of-pocket expenses was $12,000 [96] (Box 6).

Box 6 Key Points: Diabetes Mellitus in the Elderly

The WHO diagnostic criteria for diabetes: fasting plasma glucose >7.0 mmol/ or fasting whole blood glucose >6.1 mmol/L or a 2 h post-glucose load plasma glucose level >11.1 mmol/L [10].

Type 1 diabetes can occur at any age-idiopathic or auto-immune destruction of beta cells and is insulin dependent [10]; in type 2, 90–95% of diagnosed diabetics are insulin resistant.

They may present only with one or more of the geriatric syndromes, namely, falls, incontinence, decreased cognition or fatigue, lethargy or weight loss [27].

The management of diabetes in the elderly is complex, but in general the principles of management are similar to that of younger patients [28, 29].

Acute complications: diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS).

Long-standing diabetes is associated with damage and dysfunction of large (macrovascular) and small (microvascular) blood vessels resulting in damage to the various organs.

Diabetic nephropathy is the leading cause of chronic renal failure in the United States and Western countries and accounts for 40% of new cases of end-stage renal disease (ESRD) in the United States [68].

Diabetic neuropathy is common in elderly patients and occurs in little more than half of the patients with type 2 diabetes.

Aggressive management and treatment of the risk factors are crucial.

Multiple Choice Questions

1. The following are true with regard to the complications of diabetes mellitus, EXCEPT:
   A. Diabetic ketosis (DKA) is precipitated either by infection or insulin omission.
   B. In hyperosmolar hyperglycaemia syndrome (HHS), the beta-cell function is inadequate to prevent lipolysis but not hyperglycaemia.
   C. In DKA lack of insulin combined with increased catecholamines results in lipolysis ultimately resulting in ketogenesis.
   D. HHS is characterized by hyperglycaemia, dehydration, ketosis and osmotic diuresis.
2. The following are true of diabetic neuropathy in the elderly, EXCEPT:
   A. In the elderly with type 2 diabetes mellitus, >50% of men have peripheral neuropathy.
   B. The patients with proximal neuropathy are usually older than 50 years with poorly controlled diabetes.
   C. The process is generally progressive, and treatment at present is limited to alleviation of pain and associated symptoms.
   D. The longer nerve fibres are affected late and to a lesser degree than the shorter because nerve conduction velocity is slowed in proportion to the nerve's length.
3. The diagnosis of diabetes mellitus can be made with the following criteria, EXCEPT:

A. Fasting blood glucose >6.1 mmol/L
B. Fasting plasma glucose >7.0 mm/L
C. A 2 h glucose load plasma glucose >14.1 mm/L
D. A random >11.1 mm/L

4. The mechanism of action of the following antidiabetic drugs are true, EXCEPT:
   A. The sulphonylureas augment the first and second phases of insulin secretion.
   B. The biguanides antihyperglycaemic properties are attributed to decrease in the peripheral tissue insulin sensitivity.
   C. The alpha-glucosides inhibit intestinal alpha-glucosidase enzyme in the brush border to enhance the rate of carbohydrate digestion.
   D. The thiazolidinediones improve whole-body insulin sensitivity by activating the PPAR alpha-receptor.
5. The following changes are true with ageing, EXCEPT:
   A. There is a progressive impairment of glucose tolerance with advancing age.
   B. The secretion of T3 and TSH is reduced with normal ageing.
   C. There is an increase in the level of parathyroid hormone (PTH) with age.
   D. Calcitonin levels also seem to increase with age.

MCQ Answers

1=B; 2=D; 3=D; 4=C; 5=D

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Thyroid Disease in the Older Patient

48

Contents

Abstract

Thyroid abnormalities are relatively common in the general population but have important clinical implications in the elderly because of the coexisting comorbidities and increased risk of heart disease and hypercholestraemia. The symptoms of thyroid diseases are more subtle in the elderly compared to younger individuals and are often attributed to normal ageing. Thyroid dysfunction is common in the elderly and is present in more than 10% of individuals over the age of 80 years and takes the form of clinical and subclinical hypo- and hyperthyroidism, nodules and thyroid cancer. The review provides an overview of thyroid disease in the elderly, prevalence and the clinical management.

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_47

Keywords
Thyroid disease in the elderly · Hyperthyroidism · Hypothyroidism · Subclinical hypo- and hyperthyroidism · Thyroid nodules · Thyroid cancer

Introduction

Thyroid abnormalities are relatively common in the general population but have important clinical implications in the elderly because of the coexisting comorbidities and increased risk of heart disease and hypercholestraemia [1, 2]. Subclinical hypothyroidism is associated with adverse lipid profile [3, 4], endothelial dysfunction [4, 5] and increased carotid intimal thickness [6]. In the elderly the presence of clinically significant disease in geriatric institutions is between 2% and 5% [7]. The symptoms of thyroid diseases are more subtle in the elderly compared to younger individuals and are often attributed to normal ageing.

Thyroid dysfunction is common in the elderly and is present in more than 10% of individuals over the age of 80 years [8] and takes the form of clinical and subclinical hypo- and hyperthyroidism, nodules and thyroid cancer [9]. Serum TSH, free T4 and free T3 concentrations change with ageing [10–12]. T4 production declines with advancing age [13], but the serum T4 (total and free) concentration remains unchanged [14] because degradation of T4 is also reduced in the elderly [15]. Most of the T4 in the blood is attached to a protein, the thyroid binding globulin. In healthy aging the data on TSH changes are equivocal [15] but typically remains normal except for a mild decrease in both men and women [15] in extreme senescence [16]. A recent longitudinal study showed that with ageing, serum TSH increases, and there was no significant change in free T4 concentrations [17]. In males the TSH levels do not vary with age but is increased in the females after the age of 45 years, but this rise is largely eliminated when persons with thyroid antibodies are excluded [18]. The incidence of thyroid antibodies and hypothyroidism increased with age [19] and is greater in women over the age of 60 years [20], and this increase appears to be related to age-associated diseases rather than to ageing per se [21]. Whether these changes are indicative of true thyroid disease (subclinical) or merely represent physiologic changes with advancing age seems unclear [22], and hence the diagnosis of thyroid disease in the elderly can be problematical [23] (Box 1).

Box 1 Key Points. Thyroid Disorders
Thyroid abnormalities have important clinical implications in the elderly because of the coexisting comorbidities and increased risk of heart disease and hypercholestremia [1, 2].

The symptoms of thyroid diseases are more subtle in the elderly compared to younger individuals and are often attributed to normal ageing [25].

Thyroid dysfunction is common in the elderly and is present in more than 10% of individuals over the age of 80 years [8] and takes the form of clinical and subclinical hypo- and hyperthyroidism, nodules and thyroid cancer [9].

TSH changes during healthy ageing are equivocal but typically remain normal except for a mild decrease in extreme senescence [16].

The diagnosis of thyroid disease in the elderly can be problematical [23].

The diagnosis of thyroid disease in older adults is often missed or delayed because of the atypical presentation or altered clinical course. The evaluation of thyroid function in the elderly is complicated by the increased presence of acute and chronic non-thyroidal illness and use of medications [8]. Thyroid disease had not been previously recognized in 65% of those with an abnormal TSH [24]. In older patients while some of the symptoms of thyroid disease are similar to those of younger patients, it is not uncommon for them to manifest in subtle ways [25] often mimicking diseases of the heart, bowel, or a disorder of the nervous system and often attributed to ageing

[25]. In overactive thyroid, the elderly patient may present with one or two symptoms, whereas the younger patient often has multiple symptoms related to the disorder. In old age the thyroid function tests may be affected by cardiac conditions, cerebrovascular disease, diabetes mellitus, malnutrition and other conditions common in old age. Medications may interfere with thyroid function tests and mask the signs and symptoms of thyroid disorders [26]. In the elderly autoimmune, thyroiditis is the most common cause of hypothyroidism [26]. The rate of aggressive forms of thyroid cancer is higher in older than in younger patients [26] and more aggressive in men than in women [27]. The definitions based on the hormonal levels are shown in Box 2.

Box 2 Definitions (After Empson et al. [24])

Euthyroidism defined as serum TSH of 0.1–4.5 ml/UL

Overt hyperthyroidism defined as TSH of <0.1 mIU/L plus high FT4 (>25.1 pmol/L)

Overt hypothyroidism defined as increased TSH (>4.5 mlU/L) plus low FT4 (<11.5 pmol/L)

Subclinical hyperthyroidism decreased TSH <0.1 mlU/L and normal FT4 (11.5–25.1 pmol/L)

Subclinical hypothyroidism increased TSH (>4.5 mlU/L) and normal FT4 (11.5–25.1 pml/L)

Hypothyroidism

The prevalence of overt hypothyroidism is 2–5% in those above 65 years. In the Framingham study, 2.4% men and 5.9% women aged 60 and over had hypothyroidis [28]. Hypothyroidism in many has an autoimmune basis (Hashimoto's disease) [14, 26, 29]. Hypothyroidism occurring as irreversible thyroid failure is due to idiopathic hypothyroidism, from autoimmune damage to the thyroid gland (Hashimoto's disease), surgical removal of gland (Graves' disease or patients with multinodular goitre or thyroid cancer) [14, 29] and irradiation. In the elderly autoimmune thyroiditis is the most common cause of hypothyroidism [26]. Medications such as amiodarone, lithium and cytokine blockers diminish secretion of thyroid hormones [30, 31]. Proton pump inhibitors, antacids, oestrogens, phenobarbital and rifampicin can alter T4 absorption, metabolism of T4 and T3 and their transport in the serum [26]. Drugs such as dopamine, opiates and glucocorticoids decrease TSH levels [22, 26]. (see Box 3).

Box 3 Causes of Hypothyroidism

I. Primary
Idiopathic
Chronic autoimmune thyroiditis
Post-thyroidectomy
Neck radiation
Post-radioactive I2 therapy
Antithyroid agents: lithium, amiodarone
I_2 radiocontrast agents
II. Secondary
Pituitary (decreased TSH) disorders
Hypothalamic (decreased TRH) disorders

Information sources: [26, 29–31]

Clinical Manifestations

Less than one-third of the elderly patients present with the characteristic signs and symptoms (tiredness, dry skin, cold imbalance, constipation, myalgia, among others). Most present with non-specific and atypical symptoms [31] and are often attributed to ageing [32] or comorbidities associated with aging. Many of the elderly manifest non-specific symptoms which are common to the elderly such as falls, incontinence, mental confusion, loss of weight, loss of appetite and decreased mobility together with arthralgic pains, muscle pains and weakness and heart failure [23]. Myxoedematous facies and puffiness around the eyes are difficult to distinguish from the normal facial changes associated with aging. Lack of concentration, decrease in mental activity, depression and sleepiness during the day are due

Table 1 Some differences between young and elderly with hypothyroidism

	Young	Elderly
Age of onset	<65 years	>65 years
Gender	Women > men 10:1	Women > men
Prevalence, incidence	14–19/1000 females, less than 1/1000 males	5–20% females, 3–8% males, 4% undiagnosed
Cause	Autoimmune thyroiditis	Drugs, thyroidectomy, radioiodine therapy
Clinical characteristics	Tiredness, weight gain, constipation, cold intolerance, dry skin, coarse hair, hoarseness, face puffy, lethargy, heavy periods	Failure to thrive, depression, confusion, falls, walking disturbances, heart, changes of bowel habits either constipation or diarrhoea
Laboratory findings	Autoantibodies; greater in females	

Information sources: Laurberg et al. [3], Morganti et al. [20], Doucet et al. [33], Samuels [35] and Levy et al. [36]

to changes in the central nervous system, and abnormalities in the cerebellum may give rise to an ataxic gait [23]. Paraesthesias of the extremities are common and often due to carpal tunnel syndrome [23]. Doucet et al. [33] recorded four signs less frequent in the elderly, namely, chilliness, paraesahesias, weight gain and cramps. A characteristic sign is the delay in relaxation of the deep reflexes. The heart may be enlarged together with bradycardia. The electrocardiogram may show low voltage with non-specific ST changes. Not infrequently the patient may present with effusions with an effusion in the joints or in the serous cavities, pericardial, pleural and peritoneal which may give rise to diagnostic bafflement (Table 1).

Myxoedema coma is a life-threatening emergency. It occurs in patients with long-standing history of myxoedema and who have not been treated or where the medication had been discontinued during an intercurrent illness. It is often precipitated by infection, exposure to cold and use of analgesics and narcotics. The patient may present with disordered sensorium – stupor to coma associated with hypotension, hypothermia, respiratory depression and seizures [34].

Diagnosis

The measurement of sensitive thyroid-stimulating hormone (sTSH) is the best single test for the diagnosis of hypothyroidism and hyperthyroidism. It is also cost-effective. A suppressed TSH level (<0.1 nU/L) is indicative of thyrotoxicosis and an elevated TSH (>10 nU/ml) is indicative of hypothyroidism and will need further confirmation by the measurement of free T3 and T4 levels or free T3 index and free T4 index). A decrease of FT_4 and FT_4I is characteristic of all forms of hypothyroidism [34]. In primary hypothyroidism the TSH is elevated. In secondary hypothyroidism, the serum TSH level is normal with low serum FT_4I [34]. The mean cholesterol was 0.36 nmol/L higher in hypothyroid subjects than in euthyroid subjects [24, 34]. Serum thyroid antibodies are helpful in determining the cause of the hypothyroidism [34].

Treatment

The treatment of hypothyroidism of elderly patients must take into account the potential risks such as precipitating cardiac ischaemia. The most hazardous of early therapy is myocardial infarction. To minimize the risk, treatment is usually begun slowly with initial lower doses limited to 25 μg daily with increases by similar amounts at 4–6 weeks intervals [34, 37] until the laboratory tests show a gradual return of TSH to normal range. Full clinical recovery may take as long as 6 months despite the return of serum thyroxine level to normal. It is imperative gradual and cautious methods of care are required to monitor and manage the elderly so as to ensure safety and effectiveness.

Precise monitoring of TSH levels in the elderly taking thyroxine is necessary to adjust if necessary the treatment regimen. The optimal frequency of monitoring patients is unclear, and some investigators have suggested yearly monitoring with sTSH yearly. Women on long-term thyroid therapy should be monitored to keep the serum TSH levels within normal limits and the liver function tests done yearly [38]. In two recent studies, it had been shown that giving a lower dose in the very old is acceptable on the grounds that a high TSH and or low FT4 levels are associated with a lower mortality rate [39, 40]. If clinically euthyroid, a normal sTSH requires no dosage adjustments, but an undetectable sTSH suggest that there is over-replacement and the dosages reduced regardless of the T4 and FT4 levels. If the sTSH is >10 mU/L, the dosages should be increased provided the patient had been compliant. Serum T3 and T4 measurements are not necessary because serum TSH alone is reliable in detecting hypothyroidism or hyperthyroidism. Concomitant use of drugs may affect the thyroxine dosage required for adequate replacement. Ferrous sulphate, soy preparations, calcium carbonate and cholestyramine may interfere with intestinal absorption, and phenytoin, carbamazepine and rifampicin increase thyroid clearance and hence may require increased requirements of thyroxine [41].

Atrial fibrillation and or increased fracture risk can occur if there is over-replacement of thyroxine [42]. Several studies have shown significant decrease in bone mineral density in patients on thyroid therapy [34] and low or suppressed TSH levels. Oestrogen or biphosphonates have been shown to prevent osteopenia induced by thyroid hormone therapy [34, 43, 44].

For patients with severe hypothyroidism with impending or in myxoedematous coma, the approach is modified for a rapid correction. An initial dose of 0.3 mg IV levothyroxine is given followed by 0.05–0.1 mg IV daily till the patient is able to take the medication by mouth. Concomitantly 100 mg of hydrocortisone is administered eight hourly. Assisted ventilation may be required [45].

Subclinical Hypothyroidism

Subclinical hypothyroidism is characterized by mild elevation of serum TSH level with normal free thyroid hormone (T3 and T4) concentrations and absence of clinical features of hypothyroidism [35, 46]. Post-thyroid ablation and Hashimoto's thyroiditis are common causes of subclinical hypothyroidism. The patients are usually asymptomatic with no clinical signs or symptoms [47]. The management of subclinical hypothyroidism is controversial. If the TSH level is between 5 and 10 mU/L with free T3 and T4 within reference range, its progression to overt hypothyroidism is extremely rare (<5% per year) [41]. Intervention may be unnecessary and continued monitoring at 6–9 months is more appropriate. Patients with sTSH levels of >10 mU/L with subclinical hypothyroidism have shown variable rates of progression to overt hypothyroidism and those with sTSH between 5 and 10 IU/L with symptoms should be treated [48]. In one study 80% of the patients with subclinical hypothyroidism developed frank hypothyroidism in a 4-year follow-up [49]. It is advisable to commence therapy with higher levels of TSH and higher titres of anti-microsomal antibodies and higher levels of LDL-cholesterol [50].

Hyperthyroidism

The prevalence of hyperthyroidism changes very little with age. The incidence of unsuspected cases of overt hyperthyroidism ranges from 2 to 20 cases/1000 persons [7]. The causes of hyperthyroidism in the elderly are shown in Box 4. Depending on the iodine intake in most cases, Graves' disease and toxic multinodular goitre are the cause with relative proportions [20].

Box 4 Causes of Hyperthyroidism

1. Graves' disease (diffuse toxic goitre)
   (goitre, exopthalmos and peritibial myxoedema)

(*continued*)

Box 4 Causes of Hyperthyroidism (continued)
2. Toxic solitary or multinodular goitre (Plummer's disease) – more common in the elderly
3. Iatrogenic, amiodarone induced, TSH-secreting pituitary adenoma
4. Adenoma or carcinoma (follicular) of the thyroid

Clinical Manifestations

Hyperthyroidism presents with different clinical features in the elderly. The symptoms tend to be cardiovascular, gastrointestinal, neuropsychiatric and neuromuscular. The heat intolerance nervousness noted in the young may be absent in the elderly [23]. Cardiovascular system is predominantly affected, and atrial arrhythmias, heart failure and angina may dominate the clinical picture to the exclusion of the normal manifestations of thyrotoxicosis and obscure the diagnosis. Of importance is weight loss and non-specific symptoms often termed "failure to thrive" and includes loss of appetite, abdominal distress, diarrhoea, constipation or diarrhoea alternating with constipation [23]. *Apathetic thyrotoxicosis* is a well-recognized entity and characterized by apathy and weight loss, and otherwise unexplained atrial fibrillation may be wrongly classified as depression or occult malignancy. Neuropsychiatric features include listlessness, weight loss and mental confusion. Proximal and some distal myopathy with weakness may be wrongfully attributed to ageing. Trivalle et al. [51] in a study of signs and symptoms of hyperthyroidism in older and younger patients found that in more than half of the elderly patients, thecommonest signs were tachycardia, fatigue and weight loss. They found that hyperactive reflexes, increased sweating, tremor, nervousness, polydipsia and increased appetite occurred less frequently in older patients compared to younger patients. Goitre was more frequent in the younger patients (90% vs 50%) [51] (Table 2).

Diagnosis

The various types of hyperthyroidism are characterized by the overproduction of T3 and to a lesser extent T4. T3 hyperthyroidism accounts for 5% ofhyperthyroidism at all ages, and serum T4

Table 2 Some differences between young and elderly hyperthyroidism

Young	Elderly	
Age of onset	<65 years	>65 years
Peak age	20–49 years	60–69 years
Gender	Women to men: 2:1	Women > Men
Prevalence, incidence	19–27/1000 females, 1.6–2.3/1000 males	0.55–3%
		2% undiagnosed
Cause	Graves' disease (90%)	Graves' disease (70%), toxic multinodular goitre
	Goitre (90%)	Goitre (50%)
Clinical characteristics	Tachycardia, palpitations, weight loss, increased appetite, diarrhoea, sweating, muscle weakness, tremors, cardiovascular symptoms, heat intolerance, hyperactive reflexes (all of the above less common in elderly) AF with high ventricular rate	Apathetic, weight loss, anorexia, AF with slow ventricular rate, angina, congestive heart failure; may present with only one symptom – thyroid myopathy, fatigue, tiredness, confusion, cognitive impairment, dementia
Laboratory findings	Thyroid antibodies – suggest Graves' disease	T3 increase (T3 toxicosis) noted in elderly

Information sources: Chivata et al. [9], Morganti et al. [20], Goldenberg [23], Faggiano et al. [26], Samuels [35], Levy [36] and Trivalle et al. [51]

level is normal despite clinical evidence of hyperthyroidism. T3 levels could be reduced in the healthy elderly [52] but more commonly with acute or chronic illnesses (*euthyroid sick syndrome*) [53]. In the elderly serious illnesses acute or chronic may invariably lower serum T3 levels and no longer reflects thyroid activity [54]. A patient with hyperthyroidism may have normal serum T3 level. With more serious illness, T4 and free T4 index may decline into normal range.

Treatment

The treatment of choice for most elderly patients with hyperthyroidism from Graves' disease or single autonomous nodule is radioiodine therapy [23] because of the age-related risks of surgery and poor compliance. Antithyroid drugs are effective in patients with Graves' disease if compliance is good. Propylthiouracil (PTU) and metimazole are the best initial therapy. Neutropenia is the most important adverse effect and both lower granulocyte levels. It has been reported that PTU can trigger anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitides (AASV) [55]. Some of the patients have recovered on cessation of the PTU, but others had required conventional immunosuppressive therapy [55, 56].

In the case of solitary toxic nodule, radioiodine is the preferred option as drugs are slow to work in this kind of goitre. In multinodular goitre, radioiodine is not very useful for the effect is delayed and incomplete. Surgery is preferred for low-risk patients. Most of the thyroid function is brought under control first with antithyroid drugs (prophylthiouracil, methamazole) before initiating treatment with radioiodine. Symptoms of hyperthyroidism may be brought under control with adjunctive medications such as beta-adrenergic blockers (propanolol, metaprolol) unless contraindicated because the patient has cardiac failure. It may be given with antithyroid drugs before radioiodine therapy or surgery. The dosage must be individualized (Box 5).

Box 5 Treatment of Hyperthyroidism in the Elderly

Grave's disease - drugs if compliance is good.

Soliatry toxic - radio-iodine theraphy (because of age-related risks of surgery and because drugs are slow to work with this kind of goitre).

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is more common in women than in men especially in those above the age of 70 years [57]. The causes are similar to hyperthyroidism, and in addition thyroid suppression therapy is a frequent cause in the elderly [57, 58]. If reversible biochemical abnormalities due to over-replacement with thyroxine, transient subacute thyroiditis and transient iodine-induced thyrotoxicosis have been excluded, the adverse consequences of subclinical hyperthyroidism need intervention [41]. In older patients age >65 years or inthe presence of comorbidities such as atrial fibrillation or osteoporosis, treatment is mandatory [59].

Cancer of Thyroid

Introduction

Throughout the world the annual incidence rate ranges from 0.5 to 10 cases per 100,000 and a twofold and fourfold increase of new thyroid cancer in women compared to men [60]. It is estimated that in the United States 37,200 men and women (10,000 men and 27,000 women) will be diagnosed with thyroid cancer, and 1630 men and women will die of cancer of the thyroid in 2009 [61]. In England and Wales cancer of the thyroid represented 0.5% of all malignancies [62]. The incidence in the over 65 years age group appears to be increasing, and between

2.5% and 12% of differentiated cancer of the thyroid occur in this group [63, 64].The elderly are at higher risk of developing thyroid cancer which is more aggressive in men than in women [27].

Cancer of the thyroid takes four forms, papillary, follicular, anaplastic and medullary. Each has its own characteristics. About 90% of thyroid cancers originate from the follicular cells, and some develop from the parafollicular cells or C cells. Most cases occur between the ages of 25 and 65 years and more frequent in women than in men. The more aggressive forms are seen in older patients [26] and is more aggressive in men than in women [20]. There may be a history of irradiation to neck and chest especially in childhood and family history of medullary cancer of the thyroid or multiple endocrine neoplasia [26].

Symptomatology

The symptoms can vary according to the type of cancer, but some of the common symptoms are swelling in the neck, pain in the neck, difficulty in swallowing, difficulty in breathing (wheeze), frequent cough, hoarseness of voice and lymph node enlargement in the neck. Papillary cancers are generally slow growing and metastasise late to the lymph nodes in the neck, lungs and bone. Follicular cancer likewise is also slow growing but somewhat aggressive. The anaplastic cancers grow rapidly and respond poorly to treatment [65]. Medullary cancers secrete calcitonin which serves as a tumour marker and is useful in screening relatives [65].

Diagnosis

Box 6 shows some of the factors which raise suspicion of cancer of the thyroid. History of irradiation to the neck in childhood and family history of medullary cancer of the thyroid are risk factors for thyroid malignancy.

Box 6 Findings That Raise Suspicion of Malignancy

A solitary nodule in an otherwise normal gland

'Cold' nodule on thyroid scan

A hard nodule

A hard nodule attached to surrounding structures

Enlarged regional lymph nodes

Rapid enlargement of the nodule

Thyroid Nodule

Thyroid nodule can be either a solitary single nodule or a dominant nodule in a multinodular goitre.

Thyroid nodules are common. About half of the world population with normal thyroid gland contain nodules. The incidence of cancerous nodules increases with age and is greatest in men [20]. The prevalence of thyroid nodule varies according to the screening method used. It is more common in women and in the general population. It is approximately 4% and women to men ratio is 4:1 [34]. The cause is not known. The greatest risk factor is exposure to irradiation in childhood. Other risk factors include areas of iodine deficiency, pre-existing thyroid disease and family history of medullary cancer of the thyroid or multiple endocrine neoplasia (MEN) syndrome (Box 7).

Box 7 Nodular Thyroid Disease

- Solitary
- Dominant nodule

1. Thyroid scan
   To determine if hot or cold
2. Ultrasound
   To determine solitary or cystic
   (Does not add to diagnostic yield)
3. In most cases 1 and 2 are unnecessary. FNB is the most cost-effective. FNB is the most sensitive test for the detection of thyroid cancer.

About 50% of the patients with clinically detected solitary nodules have additional nodules on ultrasound [66]. Approximately only 5% of the nodules will be cancerous, and the vast majority are benign, although 10% of the population will have thyroid nodules [67]. Most adenomas are solitary lesions, and apparent multiple adenomas are often discrete nodules of a multinodular goitre [68]. Cystic degeneration of a pre-existing adenoma can present as a thyroid cyst which may be mistaken for a solitary nodule.

Diagnosis

History of irradiation to neck in childhood, a family history of medullary cancer of the thyroid, male sex and age less than 30 years and more than 50 years are risk factors for malignancy [69]. Physical examination is rarely helpful in differentiating benign from malignant nodules. The presence of enlarged lymph nodes and evidence of invasion of surrounding structures may suggest malignancy. Some of the findings that raise suspicion of malignancy is shown in Box 6. It is important to determine whether the nodule is hyperfunctioning or malignant.

i. Biochemical: Thyroid dysfunction (thyroid tests with antibodies) [70] in the presence of single thyroid nodule more usually suggest a benign process [34]. The serum TSH is suppressed in a nodule that is hyperfunctioning, and hyperfunctoning nodules have a lower risk of malignancy. A normal serum TSH in an older patient with a rapidly growing thyroid mass is suggestive of thyroid lymphoma [71]. If there is a family history of medullary thyroid cancer, serum calcitonin level should be measured [68].
ii. Thyroid imaging:
   (a) Thyroid ultrasonography: Commonly performed but rarely adds to the diagnostic yield. It determines whether the lesion is solid, cystic or complex. Certain ultrasound findings such as blurred or irregular margins, punctuate calcification and increased vascularity may suggest malignancy.

   An ultrasound guided fine needle aspiration biopsy is generally recommended.
   (b) Thyroid scanning using pertechnetate (99MTc) is done to confirm whether the lesion is 'hot' or 'cold' [34]. A non-functioning 'cold' nodule was thought to indicate increased risk of malignancy. Most nodules are cold and only 5–15% of them are malignant [71]. Hyperfunctioning nodules are rarely cancerous [34].
iii. Fine needle aspiration biopsy (FNA). FNB is the most sensitive test for the detection of cancer. In experienced hands the incidence of false-negative rate or false-positive is between 5% and 6% [34].
   (a) Benign: If the nodule is found to be benign, a follow-up examination is recommended in 6 months. If nodule had grown, then a second biopsy is recommended. Even if benign and if there is evidence of invasion (for instance, pressure on the trachea or oesophagus) of surrounding structures or for cosmetic reasons, surgery is recommended.
   (b) Malignant: If the FNA reveals malignancy, surgery is recommended to remove it.
   (c) Indeterminate: If the FNA is reported as indeterminate or suspicious, there is no way to say which nodules are benign without performing surgery. Sometimes a coarse needle biopsy may be recommended before surgery is done.
   (d) Nondiagnostic: If FNA is nondiagnostic (not enough thyroid cells), aFNA or a coarse needle biopsy is recommended [72].

Evaluation of a thyroid nodule is summarized in Fig. 1.

Impact

Thyroid hormones have important roles in the development and cognitive function [15] and are closely linked differentially by sex, race and depressive symptoms [73]. In the elderly overt

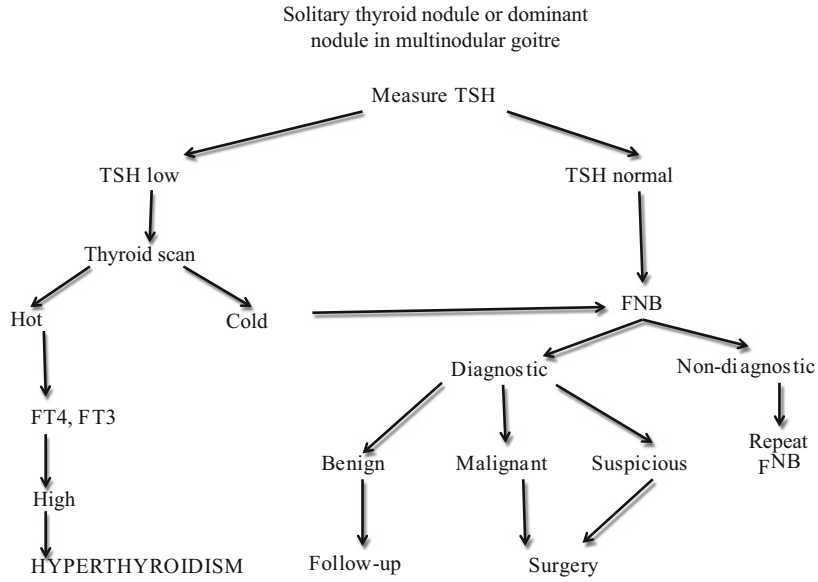

Fig. 1 Evaluation of thyroid nodule (Information sources: Mestman [34] and Mackenzie and Mortimer [71]

thyroid disorders have a negative physical and cognitive effect. Thyroid hormones may have an impact on a variety of cognitive functions [15], and overt hypothyroidism is associated with impairment of attention, memory, language and executive functions [74]. Subclinical hypothyroidism may be a predisposing factor for cognitive impairment [15], but it has been shown that in individuals aged 65 years and older, it is not associated with impairment of physical and cognitive function compared to euthyroidism [75, 76] nor associated with poor quality of life [76] (Box 8).

Box 8 Key Points. Thyroid Diseases in the Elderly

Hypothyroidism increases with age.

Thyroid disease is relatively common in older Australian women [24].

In old age thyroid function tests may be affected by cardiac conditions, cerebrovascular disease and medications, among other conditions common in old age.

Most present with non-specific and atypical symptoms [31] and are often attributed to aging [32] or comorbidities associated with aging.

Box 8 Key Points. Thyroid Diseases in the Elderly (continued)

In one study 80% of the patients with subclinical hypothyroidism developed frank hypothyroidism in a 4-year follow-up [49].

Hyperthyroidism presents with different clinical features in the elderly. The symptoms tend to be cardiovascular, gastrointestinal, neuropsychiatric and neuromuscular.

Subclinical hyperthyroidism is more common in women than in men especially in those above the age of 70 years [20]. About 1–2% of the elderly population has subclinical hyperthyroidism manifesting as suppressed TSH levels with free T3 in the reference range and often with some nodular changes.

Approximately only 5% of the nodules will be cancerous, and the vast majority are benign, although 10% of the population will have thyroid nodules [67].

Fine needle aspiration biopsy (FNA). FNB is the most sensitive test for the detection of cancer [34].

Multiple Choice Questions

1. The following are true of hypothyroidism in the elderly, EXCEPT:
   A. Recurrent falls, incontinence and mental confusion.
   B. ECG may show low voltage, non-specific ST changes and bradycardia.
   C. Brisk tendon reflexes.
   D. Muscle pains, weakness and effusion in joints.
2. The following statements regarding management of hypothyroidism in the elderly are true, EXCEPT:
   A. Full clinical recovery may take as long as 24 months despite the return of serum thyroxine levels to normal.
   B. The most hazardous of early therapy is myocardial infarction. Adage is 'go low go slow'.
   C. Patients with severe hypothyroidism with impending or in myxoedematous coma the approach is modified for a rapid correction.
   D. Concomitant use of drugs such as phenytoin, carbamazepine and rifampicin and increase thyroid clearance hence may require increased requirements of thyroxine.
3. The following statements are true of thyroid therapy for hyperthyroidism in the elderly, EXCEPT:
   A. Propylthiouracil (PTU) and methimazole are the best intial therapy for hyperthyroidism.
   B. They (i) block the oxidation of iodine, (ii) inhibit the incorporation of I_2 with tyrose and (iii) stop the coupling of compounds with T3 and T4.
   C. Both cause neutropenia.
   D. The preferred treatment for solitary toxic thyroid nodule is drugs.
4. In the management of an elderly with hyperthyroidism, the following are appropriate, EXCEPT:
   A. In Graves' disease – medication is the treatment of choice if compliance is good.
   B. In solitary toxic goitre – radiotherapy is best because of the risks of surgery.
   C. In multinodular goitre, surgery is preferred for low-risk patients.
   D. In multinodular goitre – radioiodine therapy is useful, the effect is complete, and there is no delay.
5. A 65-year-old man with a solitary thyroid nodule, the following are true, EXCEPT:
   A. TSH determines whether the nodule is hyperfunctioning or malignant.
   B. Thyroid scan determines whether it is hot or cold.
   C. Ultrasound adds considerably to the diagnostic yield.
   D. Fine needle biopsy (FNB) is the most sensitive tool for the detection of thyroid cancer.
6. The following are true of subclinical thyrotoxicosis, EXCEPT:
   A. Subclinical thyrotoxicosis is associated with moderately increased frequency of atrial fibrillation in the elderly.
   B. There is increased likelihood of osteoporosis with subclinical thyrotoxicosis.
   C. Subclinical thyrotoxicosis requires intervention.
   D. Subclinical thyrotoxicosis caused by large multinodular goitre has a prevalence of more than 50%.

MCQ Answers

1 = C; 2 = A; 3 = D; 4 = D; 5 = C; 6 = D

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Hyperparathyroidism

49

Contents

Abstract

Tertiary hyperparathyroidism occurs in patients with chronic renal failure, increases with age and is higher in postmenopausal women. The incidental finding of asymptomatic PHPT in the older patient poses problems, and there is little guidance on how to manage them. In hyperparathyroidism, the plasma calcium level is rarely >3.00 mmol/L, but the ionised calcium is almost always elevated and is a more sensitive test. In secondary hyperparathyroidism (SHPT), the abnormality in the parathyroid glands is induced by a sustained hypocalcaemic stimulus and usually associated with parathyroid hyperplasia. Tertiary hyperparathyroidism occurs in patients with chronic renal failure. The chapter reviews hyperparathyroidism and the management.

Keywords

Primary hyperparathyroidism · Secondary hyperparathyroidism · Tertiary hyperparathyroidism · Parathyroid hormone

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_48

Primary Hyperparathyroidism

Introduction

In the general population, the prevalence of hyperparathyroidism (PHPT) was established to be 1 in 1,000 [1] with the older female being the usual patient [2]. Hyperparathyroidism increases with age and is higher in postmenopausal women. There is an apparent decline in the incidence of PHPT during the last decade [3], and this progressive decline is said to be suggestive of a change in the epidemiology of the disease [4]. Parathyroid hormone (PTH) levels increase with age which is due to diminishing calcium absorption, serum 25-hydroxyvitamin D levels and diminishing renal function [5]. The calcitonin levels seem to decrease with age [6]. The incidental finding of asymptomatic PHPT in the older patient poses problems, and there is little guidance on how to manage them [2].

Clinical Manifestations

Patients may present with symptoms of (i) hypercalcaemia, lethargy, malaise and weight loss; with gastro-intestinal symptoms, nausea, vomiting, constipation, abdominal pain and ileus; or with confusion, delirium, depression, stupor, psychosis and muscle weakness; or with renal symptoms such as polyuria, nocturia and polydipsia [7]. They may present with (ii) complications of hyperparathyroidism, such as acute pancreatitis and peptic ulcer, that involve the kidney, renal calculi, nephrocalcinosis and renal failure (acute or chronic) or that of skeletal involvement such as osteoporosis, osteitis fibrous cystica, myopathy and pseudogout [7]. (iii) Occasionally, they turn up accidentally as hypercalcaemia and (iv) rarely present in an obtunded state, and (v) they may be asymptomatic. More than 30% are asymptomatic and may present non-specific cardiovascular or neuromuscular symptoms [8]. Hypercalcaemia is associated with signs and symptoms irrespective of the cause and should be distinguished from those of the underlying disorder in the course of diagnostic evaluation. There are geographical differences in the clinical manifestations. In countries where vitamin D deficiency is prevalent, PHPT may be characterised by overt severe clinical stone and bone disease [9, 10].

Physical examination is not helpful. The enlarged parathyroid glands are rarely palpable. It is reasonable to determine the serum calcium level in patients who present with non-specific symptoms for the reason that hyperparathyroidism is common and is a treatable condition. About 40% of the patients with hyperparathyroidism will demonstrate skeletal abnormalities radiographically. The radiological sign that is pathognomonic of hyperparathyroidism is subperiosteal bone resorption, usually seen on the radial aspect of the middle phalanges of the hand but can also be seen in the long bones, medial aspect of the proximal tibia, distal clavicle and sacroiliac joints. Other radiographic findings are bone cysts and 'salt and pepper' appearance of the skull. The bone cysts or 'brown tumours' that occur in the long bones and pelvis are other radiological manifestations. Osteitis fibrosa cystica areuncommon in primary hyperparathyroidism. Osteosclerotic changes usually diffuse but often involve the spine resembling the stripes on rugger jerseys, hence the name 'rugger jersey spine'. Conventional radiography may not be able to demonstrate skeletal involvement in a large number ofpatients with primary hyperparathyroidism. Non-invasive densitometry is more sensitive to demonstrate in these patients' evidence of demineralisation.

Diagnosis

In hyperparathyroidism, the plasma calcium level is rarely >3.00 mmol/L, but the ionised calcium is almost always elevated and is a more sensitive test. The serum parathyroid hormone (PTH) is elevated in both primary and secondary hyperparathyroidism and hence on its own is a good screening test (Box 1). Although PTH is usually elevated in primary hyperparathyroidism, it could be in the reference range in some cases and is best interpreted in conjunction with the ionised plasma calcium level. Other investigations include serum phosphate level which is usually low or low normal, serum alkaline phosphate a measure of bone

turnover, a urine calcium measurement useful as a marker of risk of renal calculi and creatinine and vitamin D concentration [25-OHD3] for primary hyperparathyroidism, and vitamin D deficiency frequently coexists in the elderly. Moderate range PTH values do not help to differentiate hyperplasia from adenoma nor the size of the abnormal glands [11]. For localisation of parathyroid adenomas, high-resolution ultrasound is the preferred method [12] followed by Tc-99 m-MIBI scintigraphy if the former is unsuccessful [12]. For the localisation of the suspected adenoma, CT or MRI detected earlier by scintigraphy is recommended [12]. Density measurements with three-phase contrast material enhanced CT can assist in differentiating adenomas from normal thyroid tissue and lymph nodes [13] (Box 1).

Box 1 Laboratory Findings

Serum PTH >4.0 pmolL (ref range 1.6–6.9 pmol/l).

Serum calcium >2.6 mmol/l.

ALP and PO4 usually normal abnormalities are late effects.

Treatment

The treatment of hyperparathyroidism is definite surgical removal of the abnormal gland or glands in severe hypercalcaemia or complications of the disorder. A definite cure for PHPT is parathyroidectomy [14]. There are patients who are asymptomatic where the future course of the disorder is not predictable. There are however guidelines for surgery, and these include (i) calcium level >3.00 mol/L, (ii) age under 50 years, (iii) marked hypercalciuria more than 400 mg and (v) very low bone density, T score 2.5 at any site [15]. Others have included renal calculi and nephrocalcinosis, symptoms of hypercalcaemia and parathyroid crisis. There are several groups of patients where surgery is not a clear option. In the older patient with primary hyperparathyroidism and mild hypercalcaemia, many believe conservative management is appropriate. Medical management in those with mild elevation of calcium or those unfit for surgery includes (i) adequate hydration and ambulation, (ii) calcium intake to be moderate about 1,000 mg/day, (iii) avoidance of diuretics (e.g. thiazides), (iv) oral phosphate, (v) oestrogen therapy in postmenopausal women and (vi) bisphosphonates which may be useful for arresting bone loss [16, 17]. Cinacalcet is a calcium-sensing receptor agonist, decreases PTH and calcium levels and may be used in both primary and secondary hyperthyroidism [18].

Secondary Hyperparathyroidism

In secondary hyperparathyroidism (SHPT), the abnormality in the parathyroid glands is induced by a sustained hypocalcaemic stimulus and usually associated with parathyroid hyperplasia [19]. It usually results from chronic renal failure [20] (Box 2).

Box 2 Causes of Secondary Hyperparathyroidism

Chronic renal failure [20] or occasionally malabsorption states, osteomalacia, dietary calcium deficiency and vitamin D deficiency [19].

Bisphosphonates such as alendronate and risedronate widely used to treat osteoporosis and Paget's disease commonly causes secondary hyperparathyroidism.

Secondary hyperparathyroidism is said to result from the increase in FGF-23 (fibroblast growth factor 23) concentration in chronic kidney disease [21].

FGF-23 has an important role in the regulation of phosphate-vitamin D homeostasis [21].

Diagnosis

The serum calcium range is usually low or in the lower reference range. The serum PTH level is increased, and vitamin D levels are decreased [19]. Serum phosphate levels are raised in renal disease

and low in malabsorption states. Alkaline phosphate levels are elevated [19]. To determine the cause, creatinine as an indicator of renal impairment, 25-OHD_3 to exclude vitamin D deficiency, a drug history (such as bisphosphonates) and dietary history are essential. Renal abnormalities are associated with additional soft tissue and skeletal changes of renal dystrophy.

Treatment

Management of SHPT is largely medical and includes correcting the underlying cause, inadequate calcium intake by calcium supplements (1,000–1,500 mg /daily), vitamin D deficiency with ergocalciferol, dietary phosphorus restriction with phosphate binders [21, 22] and in conjunction with a specialist. Treatment options include cinacalcet, a new phosphate binder [19]. Cinacalcet may be used in patients with secondary hyperparathyroidism in CKD patients [18, 23, 24]. Each year only about 1–2% of patients with SHPT require parathyroidectomy [25].

Tertiary Hyperparathyroidism

Tertiary hyperparathyroidism occurs in patients with chronic renal failure and long-standing secondary hyperparathyroidism and after renal transplantation [19] and in patients on dialysis and occasionally with long-standing osteomalacia.

Diagnosis

Elevation of the PTH with normal or elevated serum calcium provides the most important clues, and other biochemical findings are that of primary hyperparathyroidism such as low or low-normal phosphate and decreased vitamin D and elevated alkaline phosphate levels [19].

Treatment

In tertiary HPT, treatment is generally not indicated [19]. The pathology is hyperplasia of all four glands, and if surgery is indicated, it would be subtotal parathyroidectomy or total parathyroidectomy with autotransplantation of the parathyroid tissue into the sternomastoid muscle. In patients on dialysis, surgery is required to cure the hypercalcaemia and improve renal osteodystrophy. In successful renal transplantation, the stimulus to the parathyroids is removed, and there is spontaneous resolution of the tertiary hyperparathyroidism.

Hypoparathyroidism

The exact incidence is not known, and hypothyroidism is rare, and the estimated incidence is 4 in 100,000 people [26]. It occurs as a result injury during surgery and an overall incidence of temporary hypocalcaemias 5.4% [27]. Permanent hypoparathyroidism is rare although transient hypoparathyroidism occurs relatively frequently [28]. Prevalence is equal in men and women.

The most common cause is thyroid surgery, and auto-immune hypoparathyroidism is the next common cause [29]. Other causes include low magnesium levels and metabolic alkalosis.

Symptomatology

Symptoms include perioral and extremity paraesthesia, muscle cramp and spasm, abdominal pain, seizures, altered mental status and psychosis [29]. The nails are brittle, with dry scaly skin and cataract. The ECG shows ST and QT prolongation with terminal T-wave inversion and may proceed to ventricular fibrillation or heart block [30].

Diagnosis

Serum calcium concentration is low with increase in serum phosphate level and low parathyroid hormone. Serum magnesium levels may be low, normal or high.

Treatment

Calcium gluconate intravenously, high calcium diet and calcium supplements for some. Vitamin

D_2 (ergocalciferol) and Vitamin D_3 (cholecalciferol) – stimulates the absorption of calcium and phosphate from the intestines and promotes release of calcium from bone.

Impact

Apart from effects on the bones, PHPT can have systemic effects, cardiovascular and renal damage, confusion, dementia and mild neuropsychiatric symptoms [2]. In untreated patients with PHPT, an increased fracture rate at peripheral sites and spine has been demonstrated [14]. The older patients, frail and somewhat asymptomatic with PHPT are at high risk of developing fractures [2]. Furthermore, PHPT has an adverse effect on the cardiovascular system [2, 31] and increased risk of cardiovascular mortality [32, 33]. In PHPT, hypertension is an important risk factor and is accompanied by glucose intolerance, insulin resistance and dyslipidaemia [34]. Other harmful effects include neuropsychiatric symptoms [2] such as depression, psychosis and personality change (Box 3).

Box 3 Key Points: Hyperparathyroidism and Hypoparathyroidism

In PHPT, the plasma calcium level is rarely >3.0 mmol/l, but the ionised calcium is always elevated.

The serum parathyroid hormone (PTH) is elevated in both primary and secondary hyperparathyroidism.

The common causes of hypercalcaemia apart from PHPT are malignancy and granulomatous disease such as sarcoidosis.

There are geographical differences in the clinical manifestations of PHPT.

Secondary hyperparathyroidism usually results from chronic renal failure [20] or occasionally malabsorption states, osteomalacia, dietary calcium deficiency and vitamin D deficiency [19] and increase in FGF-23 [21].

Tertiary hyperparathyroidism results from chronic renal failure and long-standing secondary hyperparathyroidism.

Box 3 Key Points: Hyperparathyroidism and Hypoparathyroidism (continued)

Hypoparathyroidism is rare and usually follows thyroid surgery or auto-immune disorder [29]. Serum calcium is low, serum phosphate is high, PTH is low and urinary phosphate is low.

Multiple Choice Questions

1. The following in relation to primary hyperparathyroidism (PHPT) are true, EXCEPT:
   A. Majority of PHPT patients are women, and female/male ratio is 3:1.
   B. Over the past decade, there has been an increase in the incidence of PHPT.
   C. Mutations have a role in the familial forms.
   D. Parathyroid adenoma accounts for 80% of the PHPT.
2. The following clinical features in hyperparathyroidism are true, EXCEPT:
   A. Repeated attacks of acute pancreatitis.
   B. Lethargy, malaise, nausea and carpo-pedal spasms.
   C. Symptoms of diabetes insipidus.
   D. The radiological sign that is pathognomonic of hyperparathyroidism is subperiosteal bone resorption.
3. The following biochemical findings in hyperparathyroidism are true, EXCEPT:
   A. Increased serum calcium and phosphate concentrations.
   B. Increased alkaline phosphatase with bone involvement.
   C. Increased parathyroid hormone.
   D. Hypercalciuria and hyperphosphatasia.
4. The following are true of hypoparathyroidism, EXCEPT:
   A. Serum calcium is low.
   B. Serum phosphate is raised.
   C. Urinary phosphate excretion is increased.
   D. Serum parathyroid hormone is high.

MCQ Answers

1 = B; 2 = B; 3 = A; 4 = D.

Extended Matching Questions

A. Sarcoidosis
B. Malignancy
C. Vitamin excess
D. Milk-alkali syndrome
E. Tertiary hyperparathyroidism
F. Primary hyperparathyroidism
G. Hyperthyroidism
H. Familial hypocalciuric hypercalcaemia

1. A 64-year-old woman with cervical and hilar lymphadenopathy and on steroids over several months was seen with vomiting, malaise and confusion. Biochemistry showed hypercalcaemia, low parathyroid hormone, hypercalciuria, normal phosphorus and alkaline phosphatase.
2. A 68-year-old man was seen with progressive weakness, nausea vomiting and mental deterioration. He had been on calcium supplements for gastro-oesophageal efflux over several years, hypertension on thiazide and had renal insufficiency. The biochemical findings were elevated serum calcium and bicarbonate, low parathyroid hormone, normal phosphate and alkaline phosphatase.
3. A 64-year-old man with a terminal illness was seen with loss of weight, malaise and confusion. Biochemistry revealed hypercalcaemia, normal parathyroid hormone and vitamin D levels, raised alkaline phosphatase and increased urinary phosphate. The parathyroid hormone-related peptide (PTHrP) was elevated.
4. A 67-year-old man who was asymptomatic was found to have elevated serum calcium. The parathyroid hormone (PTH) was elevated. Phosphate and alkaline phosphatase were normal, and the urinary calcium was low.

EMQ Answers

1 = A; 2 = D; 3 = B; 4 = H

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Part X

Electrolyte Disturbances and Disorders of Mineral Metabolism in the Elderly

Elderly people are particularly prone to electrolyte imbalance. Hyponatremia is the most common electrolyte disorder in elderly people and is the commonest electrolyte abnormality seen in clinical practice. Hypernatremia is less common than hyponatremia but with a high mortality of 40–60%. Hypokalemia is found in 20% of hospitalized patients. The high morbidity and mortality due to hypokalemia is associated cardiac arrhythmias and sudden cardiac death. Hyperkalemia is a frequent occurrence in hospitalized patients with a reported incidence of 1.1 to 10 patients per 100 hospitalized. Malignancy (45%) and hyperparathyroidism (16.5%) are the most common causes of hypercalcemia and malignancy accounts for about 65% in the hospital. Part X reviews the main groups of electrolyte disturbances and provides an overview of their prevalence and mechanisms followed by their effects and adverse effects and clinical management.

Disorders of Sodium

50

Contents

Abstract

The elderly are more prone to disorders of sodium metabolism because of the age-related decrease in the percentage of body water content because smaller distribution of water balance will give rise to greater change in serum sodium concentration. About 11.3% of geriatric patients are hyponatraemic. Hypernatraemia is less common than hyponatraemia but with a high mortality of 40–60%. The chapter discusses the mechanisms underlying the disorders of sodium metabolism, their clinical manifestations and management.

Keywords

Chronic hyponatraemia · Hypernatraemia · Aldosterone · Antidiuretic hormone/arginine vasopressin · Antidiuretic hormone

Hyponatraemia

Introduction

About 11.3% of geriatric patients are hyponatraemic [1]. The incidence of general hospital patients with hyponatraemia is about 1% [2]. If serum sodium concentration less than 135 mEq/l is considered as a

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_50

cut-off, the prevalence of chronic hyponatraemia will be 20% among the residents in aged care facilities [3]. The hormones aldosterone, antidiuretic hormone/anginine vasopressin (ADH/AVP) and anti-natriuretic peptide (ANP) regulate the fluid and electrolyte balance and partly control the changes in fluid balance in the elderly [4]. In the elderly, the secretion of aldosterone is altered [4], and ANP is increased in the elderly about fivefold [5]. In the elderly, changes in dilution and concentration of the urine are dueto relative insensitivity of antidiuretic hormone (ADH) in the cortical collecting ducts. Despite losing 20–25% of the original kidney volume, older individuals maintain body fluid haemostasis under most circumstances [6]. However, the elderly are more prone to disorders of sodium metabolism because of the age-related decrease in the percentage of body water content because smaller distribution of water balance will give rise to greater change in serum sodium concentration [7].

Hyponatraemia can be classified as hypovolaemic, euvolaemic or hypervolaemic according to the volume status [8] or classified according to the plasma osmolality, as isotonic, hypertonic or hypotonic [9]. Hypotonic hyponatraemia thereafter can be further classified according to the volume status [9]. In hypovolaemic hyponatraemia, the decrease in total body sodium is greater than the decrease in total body water. In euvolaemic, there is increase in total body water with normal body sodium, and in the hypervolaemic, there is increase in total body water with increase in the total body sodium. The hyponatraemias can be classified pathophysiologically as hyponatraemia due to non-osmotic hypersecretion of vasopressin (hypovolaemic, euvolaemic and hypervolaemic) [8, 10, 11] and hyponatraemia of nonhypervasopressinaemic origin (pseudohyponatraemia, water intoxication and cerebral salt wasting syndrome) [11–13] determined by their plasma osmolality, glucose, lipids and proteins [11]. Hyponatraemia is considered as ‘chronic’ if it develops over 48 h or of unknown duration [9] and is frequently multifactorial [14].

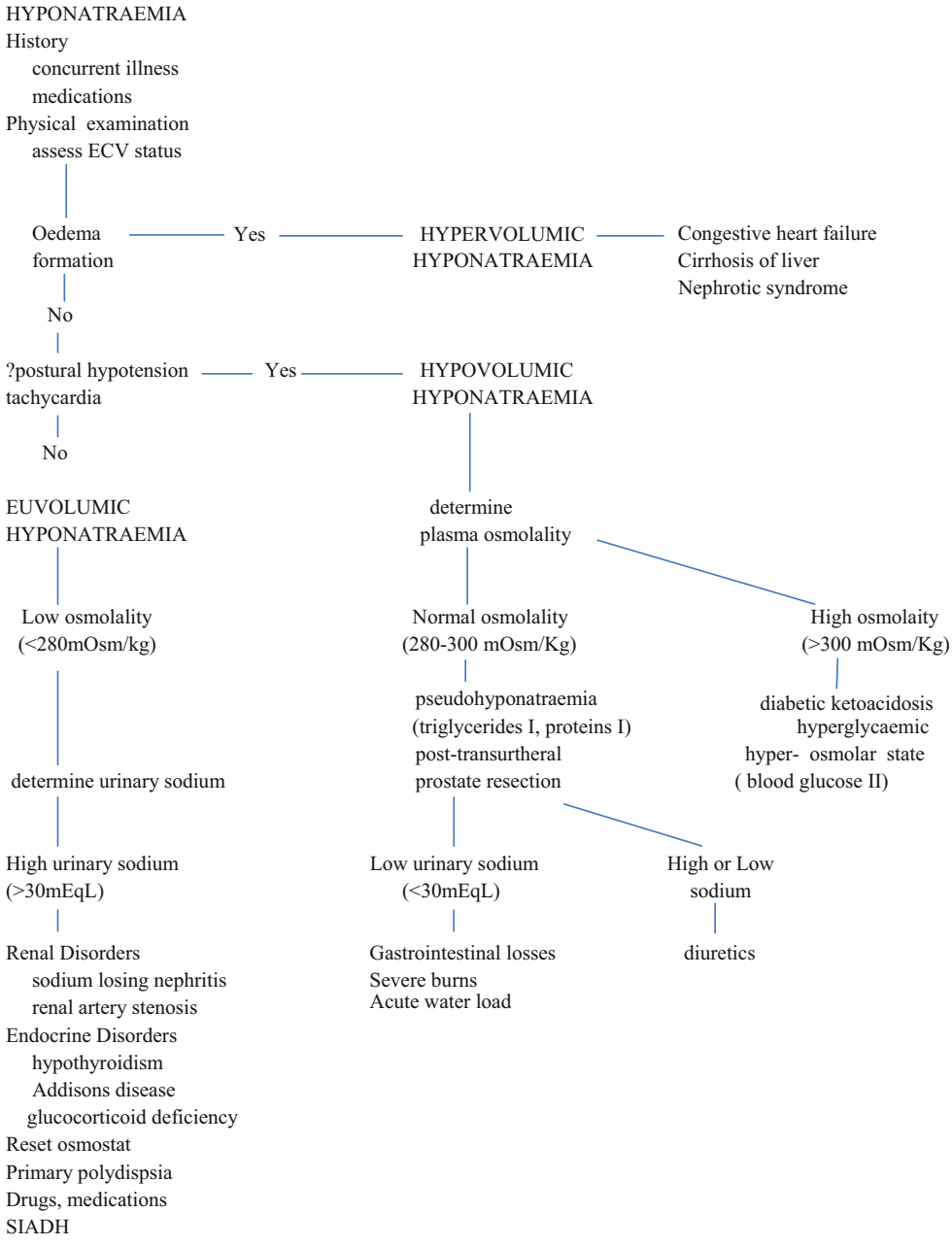
Symptomatology

Patients with mild hyponatraemia are almost always asymptomatic. The first symptoms with (Na 125–130 m/L) are feeling of nausea, weakness, tiredness, headache, nausea, vomiting, muscle cramps [15] and obtundation, or it can present with a wide variety of symptoms and may be a clue to an underlying major disease process [16]. Severe hyponatraemia (less than 115meqL) is usually associated with central nervous system symptoms such as confusion, seizure and coma and can be life-threatening [15, 17]. The elderly with hyponatraemia may present with frequent falls and gait disturbances. Even mild hyponatraemia has been associated with increased mortality and risk of falls and fractures [18]. Acute severe hyponatraemia can cause substantial morbidity and mortality. Mortality is higher in patients with wide range of underlying disorders. Patients with chronic hyponatraemia are often asymptomatic irrespective of the degree of hyponatraemia and symptoms occur if there is an acute exacerbation or sodium falls below 110 m/L [19].

Differential Diagnosis

A history of concurrent illness and medication use and a physical examination of extracellular fluid volume may provide useful clues as to the pathogenesis of hyponatraemia [20]. The first step is the measurement of plasma osmolality, glucose, lipids and proteins. Hyponatraemia with a high plasma osmolality (300 mOsm/kg or more) is caused by hyperglycaemia, while a normal (280–300 mOsm/kg) plasma osmolality indicates pseudohyponatraemia or post-transurethral prostatic resection syndrome (Algorithm 1). In pseudohyponatraemia, there is a spurious low sodium concentration due to an increase in the nonaqueous constituents of plasma such as hypertriglycerides or in hypoproteinaemia [12, 13, 19].

For further differential diagnosis of hyponatraemia, the measurement of urine sodium concentration and urine osmolality will provide useful information. Low osmolality (serum osmolarity less than 280 mosm/kg) with high urinary



Information sources: Goh [8], Millionis et al [20].

Algorithm 1 Hyponatraemia

osmolality (>100 mosm/kg) can be caused by SIADH, medications, renal disorders and endocrine deficiencies [21]. Low plasma osmolality with a high urine osmolality in the absence of diuretic use and endocrine disorders [21] confirms the diagnosis of SIADH [11, 22]. Low urinary sodium is caused by gastrointestinal losses, acute water overload and severe burns. A urine sodium

level of less than 20 mmol/L is indicative of hypovolaemia, whereas a level greater than 40 mmol/L is suggestive of SIADH. In SIADH, urea is typically low [23], and this is less specific for the elderly for whom lower clearance of urea accounts for higher values [24]. In hyponatraemia of heart failure and liver cirrhosis, there are oedema, low blood pressure and slightly elevated plasma measurements [23].

Treatment

Treatment will very much depend on the urgency, that is, severity of the hyponatraemia and symptoms, concurrent illness, whether it is acute or chronic (when it lasts for more than 48 h) and the presence and degree of hypotension [4]. In all cases with hyponatraemia, the cause should be identified, in some it is obvious (for instance, thiazide-induced hyponatraemia), and in some others further assessment may be necessary.

In acute severe hyponatraemia, sodium less than 115 mmol/L can cause seizures, irreversible neurological damage and death [15]. Treatment should be immediate because of the risk of cerebral oedema and hyponatraemic encephalopathy [8]. It entails the pace and degree of correction. It has to be done slowly because drastic change in sodium level can cause seizures, coma and central pontine myelinolysis (CPM). CPM seems to occur 1–6 days after correction and is permanent [23] with quadriparesis and weakness of the face and tongue. Normo-/hypernatraemia should be avoided in the first 48 h, and the initial correction rate should not exceed 1–2 mmol/l per hour [25, 26]. Hypertonic (3%) saline is available for treatment of severe symptomatic hyponatraemia, and 250 mg should be infused slowly and serum sodium checked 10 h later. The amount is repeated to maintain a rise in serum sodium within 10 meq/L/24 h.

In euvolaemic hyponatraemia, fluid and water restriction (less than 1–1.5 L per day) is the preferred treatment for mild and moderate SIADH. Occasionally the fluid and water restriction may be too demanding, and a combination of frusemide and increased salt intake is required [27]. In patients with hypovolaemic hyponatraemia, the precipitating causes such as gastrointestinal losses, adrenal insufficiency and diuretic abuse should receive due consideration with accompanying fluid therapy. In patients with hypervolaemic hyponatraemia, fluid and sodium restriction is the preferred treatment together with treatment of the precipitating heart, liver or renal disease. Loop diuretics can be used in oedematous hyponatraemic states [8]. In patients with cardiac failure, it can be used in conjunction with captopril or other ACE inhibitors.

In chronic hyponatraemia, removal of the underlying cause may be sufficient. In asymptomatic patients with chronic hyponatraemia, fluid restriction with monitoring should be sufficient [8, 9]. In patients with persistent severe hyponatraemia who find fluid restriction irksome, demeclocycline (dosage 600–1,200 mg daily) [8] or lithium or furosemide and salt is supplemented [10]. Demeclocycline induces enough free water excretion to allow such patients to loosen on their water intake. Demeclocycline should be used with caution in patients with cirrhosis (has been associated with acute renal failure) or renal insufficiency [28]. Loop diuretics are useful in oedematous hyponatraemic states and chronic SIADH [8].

The pressor and antidiuretic effects of vasopressin are antagonised by non-peptide vasopressin antagonists called vaptans, and there are three subtypes of VPA receptors, namely, V1a, V1b and V2 [29]. Free water elimination without affecting the electrolyte excretion are the main attributes of the vaptans [29]. Vasopressin receptor antagonists such as lixivaptan and tolvaptan and the V2 + V1a receptor antagonist conivaptan [11] may provide better treatment in the future [23]. They lead to increased serum sodium by fostering the electrolyte – sparing excretion of free water [11].

Hypernatraemia

Introduction

It is less common than hyponatraemia but with a high mortality of 40–60% [29]. In hospitalised patients, about 1% have a serum sodium higher than 150 mmol/l [30], and the frequency ranges

between 0.3% and 3.4% [30, 31]. With increasing age, the physiological responses to water deprivation may be of particular interest in understanding the pathogenesis of hypernatraemia in the elderly [32]. There is a decrease in the percentage of total body water with ageing. Hypernatraemia is classified as hypovolaemic, euvolaemic and hypervolaemic according to the state of hydration and sodium content [33]. The causes of hypernatraemia are shown in Box 1.

Box 1 Causes of Hypernatraemia

I. Hypervolaemic hypernatraemia
   - Mineralocorticoid excess
   - Adrenal tumours secreting deoxycorticosterone
   - Adrenal hyperplasia
   - Iatrogenic
   - Administration of hypertonic fluid

II. Euvolaemic hypernatraemia
   - Central diabetes insipidus
   - Nephrogenic diabetes insidious
   - Reset osmostat
   - Iatrogenic
   - Primary hypodipsia (geriatric)

III. Hypovolaemic hypernatraemia
   - Gastrointestinal losses
   - Dermal losses – burns and excessive sweating(endurance sportsmen/women)
   - Loop diuretics
   - Osmotic diuresis (urea, glucose)
   - Renal disease

Information sources: Rudolph et al. [34] and Patient.co.uk [35]

Symptomatology

Thirst is an important symptom. Delirium, seizures or coma may result. Subarachnoid and subcortical haemorrhage are frequent autopsy findings. Urine osmolality is the most useful test to determine the cause of the hypernatraemia.

Treatment

Patients who are hypervolaemic may need a loop diuretic such as frusemide to reduce excess volume [36] and dextrose 5% in water solution. Patients with euvolaemic hypernatraemia should be treated with oral water administration or intravenous 5% dextrose solution. Those who are hypovolaemic should initially be treated with IV isotonic saline, and once volume is restored, this should be changed to ½ N saline with dextrose. Once stabilised, free water deficits can be restored orally or intravenously [36]. The electrolyte levels have to be frequently determined during therapy. The water deficit is calculated using the equation Water deficit = Total body weight × (1 − current[Na+]/140) [36]. Total body weight = 0.6 × weight(in Kg) for male patients or 0.5 × weight (in kg) for female and obese patients [36].

Impact

Hyponatraemia is the most common electrolyte disorder in elderly people [37, 38] and is the commonest electrolyte abnormality seen in clinical practice [39, 40]. Hyponatraemia affects one in five hospitalised patients [5] and is associated with longer hospital stay [37, 41], poor clinical outcome and increased mortality [41]. Its prevalence is higher in frail older people [41] and in patients with fragility fractures (EPFF) [41]. Hyponatraemia is associated with higher frequency of gait and attention deficits resulting in falls [80], hip fractures, osteoporosis and cognitive dysfunction [37].

Symptomatic severe hyponatraemia can be life-threatening [37] and is associated with high morbidity and mortality [41, 42]. It is well known that even mild asymptomatic hyponatraemia is associated with prolonged hospital stays and institutionalisation [37]. In ambulatory elderly, mild hyponatraemia is associated with bone fracture [43] due to bone demineralisation with increased risk of falls due to gait instability and attention deficits [43]. Chronic hyponatraemia even mild can cause cognitive [44] and motor

impairment [42], gait disturbances, attention deficits [43], falls and fractures [44] (Boxes 2 and 3).

Box 2 Key Points: Hyponatraemia

Hyponatraemia categorised as (i) hyponatraemia of non-osmotic hypersecretion of vasopressin (hypervolaemic/euvolaemic/hypovolaemic) [7, 9, 10] and (ii) hyponatraemia of non-hypervasopressinaemic origin [10–12].

Hyponatraemia with a high osmolality (300 mOsm/Kg or more) is caused by hyperglycaemia.

A normal plasm osmolality indicates pseudohyponatraemia of post-transurethral prostatic resection syndrome.

Hyponatraemia with low plasma osmolality (<270 mosm/kg with high urine osmolality and >100 mosm/kg in the absence of diuretic) confirms the diagnosis of SIADH [10, 21].

A urine sodium level of less than 20 mmol/l is indicative of hypovolaemia, whereas a level greater than 40 mmol/l is suggestive of SIADH [22].

The initial correction rate should not exceed 1–2 mmol/l per hour [24, 25].

Drastic change in the sodium can cause seizures, coma and central pontine myelosis.

Box 3 Key Points: Hypernatraemia

Hypernatraemia can be associated with hypervolaemia, euvolaemia and hypovolaemia [33].

Urine osmolality is the most useful test to determine the cause of the hypernatraemia.

Hypervolaemic patients will need a loop diuretic (frusemide) and 5% dextrose [36].

Euvolaemic patients oral water or 5% dextrose solutions.

Hypovolaemic patients IV isotonic solution initially [36].

Multiple Choice Questions

1. The following are true of hyponatraemia except:
   A. Severe hyponatraemia is associated with confusion, seizure and coma.
   B. A urine sodium level of less than 20 mmol/l is indicative of hypovolaemia, whereas a level greater than 40 mmol/l is suggestive of SIADH.
   C. Serum osmolality less than 280 mOsm/kg with high urine concentration can be caused by SIADH, medications, renal disorders and endocrine deficiencies.
   D. In SIADH, the urea is typically high.
2. The following in the management of severe hyponatraemia are true except:
   A. Correction of severe hyponatraemia has to be done slowly for drastic changes in sodium level can cause seizures, coma and central pontine myelosis (CPM).
   B. The initial correction rate should not exceed 10–20 mmol/per hour.
   C. CPM seems to occur 1–6 days after correction and is permanent.
   D. The serum sodium level is checked to maintain a rise in the serum sodium within 10 meq/l/24 h.
3. The following relating to hypernatraemia are true except:
   A. Hypernatraemia is more common than hyponatraemia but with a low mortality of 4–6%.
   B. Hypervolaemic hypernatraemia may need a loop diuretic and dextrose 5% in water solution.
   C. Hypervolaemic hypernatraemia is treated with IV isotonic saline and once volume is restored changed to 0.05 N saline.
   D. Subarachnoid and subcortical haemorrhage are frequent autopsy findings.

MCQ Answers

1 = D; 2 = B; 3 = A

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Disorders of Potassium

51

Contents

Abstract

The high morbidity and mortality due to hypokalaemia are associated with cardiac arrhythmias and sudden cardiac death. Severe hypokalaemia causes cardiac arrhythmias, general discomfort, irritability, muscle pain, generalised weakness and paralysis. Treatment begins with determining the cause followed by alleviating the underlying disorder, potassium deficit estimated from the plasma or serum concentration. Hyperkalaemia is a frequent occurrence in hospitalised patients with a reported incidence of 1.1–10 patients per 100 hospitalised. The chapter discusses the mechanisms underlying the disorders of potassium metabolism, their clinical manifestations and management.

Keywords

Hypokalaemia · Hyperkalaemia · Cardiac arrhythmias · Sudden cardiac death · Magnesium deficiency

Hypokalaemia

Introduction

It is found in 20% of hospitalised patients [1]. The high morbidity and mortality due to hypokalaemia are associated with cardiac arrhythmias and sudden cardiac death. Excretion of potassium is increased by aldosterone, high delivery of sodium to the collecting duct (e.g. diuretics), high urine flow (osmotic diuresis) and delivery of negatively

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_51

charged ions to the collecting ducts (e.g. bicarbonate) [2]. Hypokalaemia is due to shift into the cells and may be caused by medications, normal dysregulation or raised blood pH. Magnesium deficiency is common in hospitalised patients due to dehydration and increased loss. It can cause severe hypokalaemia by increasing potassium loss. The exact mechanism remains unclear [3]. A low potassium concentration has been found in 10–40% of patients with thiazide diuretics [4]. Chronic diarrhoea, excessive sweating or severe burns can cause marked potassium loss [5]. Box 1 shows the causes of hypokalaemia.

Box 1 Causes of Hypokalaemia

i. Inadequate intake
ii. Increased renal loss
    Medications, e.g. diuretics
    Primary or secondary hyperaldosteronism
    Exogenous glucocorticoids/mineralocorticoids
    Hypomagnesaemia
iii. Increased extrarenal loss
    Gastrointestinal – vomiting, diarrhoea
    Laxatives and diuretics
    Dermal loss – burns, excessive sweat
iv. Transcellular shift
    Alkalines
    Beta-adrenergic agonists
    Insulin administration

Information sources: Lederer et al. [2], Schulman and Narines [4] and Unwin et al. [5]

Clinical Manifestations

Patients with mild hypokalaemia may have no symptoms. More severe hypokalaemia causes cardiac arrhythmias, general discomfort, irritability, muscle pain, generalised weakness and paralysis. In addition patients with severe hypokalaemia can develop muscle necrosis (rhabdomyolysis). Potassium depletion predisposes to serious tachyarrhythmias. The electrocardiogram may initially show T wave flattening or inverted T waves. Prominent U waves appear as QT prolongation and ST depression and first- or second-degree block of the Wenckebach type [6, 7]. Both mild and severe hypokalaemia can induce cardiac arrhythmias, ventricular arrhythmias (premature ventricular contractions, torsade de pointes, ventricular fibrillation) and atrial arrhythmias (premature atrial beats and atrial fibrillation). Muscle weakness, rhabdomyolysis, cardiac arrhythmias, impaired urinary concentrating ability and glucose intolerance are some of the complications of hypokalaemia [8].

Treatment

Treatment begins with determining the cause followed by alleviating the underlying disorder, potassium deficit estimated from the plasma or serum concentration [5]. In severe hypokalaemia (serum K <2.6 mmol/L), intravenous potassium as potassium chloride is given. The rate should not exceed 20 mmol per hour. Cardiac monitoring is followed by a repeat of the potassium level in 1–3 h together with workup to identify aetiology. Oral potassium supplements include potassium chloride (40–100 mmol/day in divided doses), potassium phosphate (in patients with concurrent hypophosphataemia) and potassium bicarbonate (in patients with acidosis). Potassium tablets can remain in the lower oesophagus for some time and could cause ulceration; hence it should be taken with plenty of fluid and avoided just before going to bed [5]. Serum potassium level is difficult to replenish if serum magnesium level is also low, and it may be necessary to replenish both. Patients on digoxin should have digoxin level done. Treatment includes proper diet, potassium supplements and IV solutions. Foods such as bananas, oranges, avocados, sweet potatoes and spinach are rich in potassium (Box 2).

Box 2 Key Points: Hypokalaemia

The vast majority of cases with hypokalaemia are related to diuretics especially loop diuretics commonly used in clinical practice.

(*continued*)

Box 2 Key Points: Hypokalaemia (continued)

Magnesium deficiency can cause severe hypokalaemia by increasing potassium loss.

The ECG initially shows flattened or inverted T waves. Prominent U waves appear with QT prolongation [7, 8].

Foods such as bananas, oranges, avocados, sweet potatoes and spinach are rich in potassium.

Hyperkalaemia

Introduction

Hyperkalaemia is a frequent occurrence in hospitalised patients with a reported incidence of 1.1–10 patients per 100 hospitalised [9, 10]. A common cause is excessive potassium supplement and other causes are hypoadrenalism or renal failure [11]. Medications [12] used for cardiovascular disease in a setting of impaired glomerular filtration rate commonly cause true elevations in serum potassium [13] (Box 3).

Box 3 Common Causes of Hyperkalaemia

Intake consumption of too much potassium salt

Renal diseases

Drugs and medications, e.g. diuretics

Addison's disease

Injury to muscle and other tissues

Acidosis

Burns

Infections

Clinical Manifestations

The clinical presentation to a great extent correlates with the severity of the hyperkalaemia. In the mild cases, the patients are asymptomatic. More severe hyperkalaemia presents with generalised weakness, nausea, vomiting, tingling of the extremities, numbness and paralysis and intestinal colic [14]. It affects the heart causing arrhythmias [14] including cardiac standstill and sudden death. In the mild to moderate severity, the electrocardiographic changes may be subtle and limited to peaking of the T waves. Progressive hyperkalaemia shows prolongation of the PR with disappearance of the P wave and marked widening of the QRS [15, 16]. In the extreme the QRS degenerates into a sine wave followed by ventricular fibrillation or ventricular asystole [15]. Although ECG is highly specific for hyperkalaemia, treatment of hyperkalaemia based solely on the ECG will lead to mistreatment in at least 15% of patients [17].

Treatment

In mild hyperkalaemia (<K 6 mmol/L), ceasing the offending drug (ACE inhibitors, ARBs, NSAIDs, K-sparing diuretics) would suffice. In patients with renal failure, acute or chronic treatment should be initiated earlier when the serum K level is more than 5 mmol/L. If there are no ECG abnormalities, cation-exchange resins mixed with sorbitol should be used if hyperkalaemia is not life threatening. Sodium polystyrene sulphonate in 100–200 ml 30% sorbitol can be given 15 g every 6 h orally or 30–60 g by retention enema [18]. Resin mixed with water (and not with sorbitol) can be repeated hourly for rapid removal of potassium. Enemas can cause rectal ulcerations [19].

In severe cases (K >6 mmol/L), therapy has to be aggressive. The following should be given in rapid sequence: (i) IV administration of calcium gluconate 10% 210 ml intravenously over 5–10 min and repeated when necessary [14, 20], (ii) ten units of regular insulin by rapid push followed immediately by 50 ml of 50% dextrose by rapid infusion and (iii) inhalation of beta2-adrenergic agonist over 20 min. The duration of action is about 2–4 h depending on the type of agonist used. In patients with renal failure if emergency treatment is ineffective, haemodialysis should be instituted which is most effective [21]. Elderly patients are at risk of developing hyperkalaemia when they are on certain medications, and hence potassium levels should be determined at appropriate intervals [22].

Impact

Hyperkalaemia can cause sudden death due to cardiac arrhythmias (Nat Kid Foundation) [23]. Compared to 2–3% in the general population, the frequency of hyperkalaemia could be as high as 40–50% in patients with chronic kidney disease [24]. Even within 1 day of mortality, the odds of mortality are increased with an episode of hyperkalaemia in patients with hyperkalaemia [25] (Box 4).

Box 4 Key Points: Hyperkalaemia

Most cases of hyperkalaemia are due to prescription of diuretics and drugs [12] such as NSAIDs, the angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) in conjunction with potassium-sparing attributes.

In mild to moderate hyperkalaemia, the changes on the ECG may be subtle and limited to peaking of the T wave.

Although ECG is highly specific for hyperkalaemia, treatment of hyperkalaemia based solely on the ECG will lead to mistreatment in at least 15% of patients [17].

Progressive hyperkalaemia shows prolongation of the PR with disappearance of the P wave and marked widening of the QRS [15, 16]. In the extreme, the QRS degenerates into a sine wave followed by ventricular fibrillation or ventricular asystole [15].

Multiple Choice Questions

1. The following with hypokalaemia are true EXCEPT:
   A. Three mechanisms associated with hypokalaemia are (i) dietary deficiency, (ii) increased excretion and (iii) transcellular shift.
   B. Magnesium deficiency can cause severe hypokalaemia by increasing potassium loss.
   C. The high morbidity and mortality due to hypokalaemia are associated with cardiac arrhythmias and sudden cardiac death.
   D. The electrocardiogram initially may show subtle and limited to peaking of the T waves.
2. The following in the management of hypokalaemia are true, EXCEPT:
   A. If the magnesium level is also low, it will be difficult to replenish serum potassium level.
   B. The rate of intravenous potassium given as potassium chloride should not exceed 20 mmol/h.
   C. Patients on digoxin should have their digoxin level done.
   D. Avocados, spinach and sweet potatoes are poor in potassium.
3. The following in relation to hyperkalaemia are true EXCEPT:
   A. Most cases of hyperkalaemia are due to diuretics, NSAIDs, ACEIs and ARBs in conjunction with potassium-sparing attributes.
   B. Severe hyperkalaemia causes cardiac arrhythmias and sudden death.
   C. With severe hyperkalaemia in the extreme, the QRS degenerates into a sine wave followed by ventricular fibrillation or ventricular asystole.
   D. Potassium level is normally regulated around a narrow range of 3.5 and 6.5 mmol/L.
4. The following in the management of hyperkalaemia are true EXCEPT:
   A. In patients with renal failure acute or chronic, treatment should be instituted when the serum K level is more than 7 mmol/L.
   B. In patients with renal failure if emergency treatment is ineffective, haemodialysis should be instituted.
   C. Sodium or calcium polystyrene sulphonate in sorbitol can be given orally or by retention enema.
   D. In severe cases, the following are given in rapid sequence: calcium gluconate 10% IV, regular insulin 10 units by rapid push with 50 ml of 50% dextrose rapid infusion and inhalation of a beta2-adrenergic agonist.

MCQ Answers

1 = D; 2 = D; 3 = D; 4 = A

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Disorders of Calcium Metabolism

52

Contents

Abstract

Malignancy and hyperparathyroidism are the most common causes of hypercalcaemia, and malignancy accounts for about 65% in the hospital. Patients with acute hypercalcaemia usually present with gastrointestinal symptoms such as nausea, vomiting, anorexia and dehydration. Hypercalcaemia may produce ECG changes. Hypocalcaemia has a prevalence of 85% in ICU and 18% of all hospital patients. Patients with hypocalcaemia are symptomatic (tetany, seizures) or at high risk of developing complications. The chapter discusses the mechanisms underlying the disorders of calcium metabolism, their clinical manifestations and management.

Keywords

Hypercalcaemia · Hypocalcaemia · Hyperparathyroidism · Malignancy

Hypercalcaemia

Introduction

In hospitalized patients there is a large variation in the prevalence of hypercalcaemia ranging from 0.17% to 2.92% and in normal populations 1.07% and 3.9% [1]. Malignancy (45%) and hyperparathyroidism(16.5%) [1, 2] are the most common causes of hypercalcaemia [3], and malignancy accounts for about 65% in the hospital [4].

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_52

Other causes of hypercalcaemia in the elderly include abrupt immobilization with previously elevated skeletal remodelling activity and hyperthyroidism [5].

Clinical Manifestations

Patients with acute hypercalcaemia usually present with gastrointestinal symptoms such as nausea, vomiting, anorexia and dehydration. Other manifestations include polydipsia and polyuria. There may be grades of disordered sensorium, confusion, stupor or coma [6]. Those with chronic hypercalcaemia usually complain of constipation, dyspepsia and abdominal pain due to pancreatitis [6]. The blood pressure may be elevated. There may be generalized weakness and evidence of nephrocalcinosis or nephrolithiasis (Box 1).

Box 1 Manifestations and Complications of Hypercalcaemia

General
Lethargy, weakness, malaise, dehydration
Gastrointestinal
Nausea, vomiting, anorexia, constipation, abdominal pain
Ileus, acute pancreatitis, peptic ulcer
Central nervous system
Confusion, delirium, emotional lability, depression, muscle weakness, psychosis, stupor and coma
Renal
Polyuria, polydipsia (nephrogenic diabetes insipidus)
Nocturia
Nephrocalcinosis, calculi, acute or chronic renal impairment
Cardiovascular
Cardiac arrhythmias, ECG changes (shortened QT interval)
Digitalis sensitivity
Musculoskeletal
Myopathy, osteoporosis, osteitis fibrosa cystica, pseudogout

Information sources: Koh [6] and Turhan et al. [8]

Hypercalcaemia may produce ECG changes. The QT interval may be shortened, and in some cases the PR interval is prolonged. With severe hypercalcaemia, the QRS interval may lengthen, T waves may flatten or invert, ST elevation may occur [7], and a variable degree of heart block may develop. In hypercalaemia ST elevation may occur in leads V1–V3 with transient Q waves mimicking acute myocardial infarction; these changes however return to normal with treatment of the hyperkalaemia [8, 9].

Evaluation

A complete history should include the clinical manifestations of hypercalcaemia, possible causative disorders and medications. The measurement of the PTH in the serum gives the direct indication of parathyroid function. A reference range is 1.6–6.9 pmol/L. A serum PTH level >4.0 pmol/L and the presence of serum calcium >2.6 mmol/L are indicative of primary hyperparathyroidism. If in the presence of hypercalcaemia and suppressed PTH, hyperparathyroidism is unlikely.

PTH values <2.0 pmol/L are indicative of an extraparathyroid cause for the hypercalcaemia. If PTH is suppressed in the face of elevated calcium level, the possibilities are that it may be associated with:

(i) Malignancies due to extensive bone destruction resulting from osteolytic metastases or caused by PTH-related protein (PTHrP). The gene that produces this protein is present in a many malignancies.
(ii) Vitamin D excess shows elevation of serum calcium and phosphate and a suppressed PTH. Common cause is overdosage with calcitriol.
(iii) Granulomatous disorders have high levels of calcitonin. Serum phosphate levels tend to be low or normal in primary hyperthyroidism and hypercalcaemia of malignancy. It is also elevated in hypercalcaemia secondary to vitamin D disorders or hyperthyroidism.

Management

Several measures are available in the treatment of hypercalcaemia such as fluid repletion normal saline 2–4 L/24 h, loop diuretics (IV frusemide 6–12 hourly), bisphosphonates (pamidronate, ibandronate and zoledronate), calcitonin, mithramycin, gallium, glucocorticoids and dialysis [6].

Acute primary hyperparathyroidism requires parathyroidectomy. Pharmacological treatment is required in some cases of hyperparathyroidism presenting with symptoms of hypercalcaemia. The other common cause of hypercalcaemia is malignancy. The cornerstone of therapy is to inhibit osteoclastic bone resorption. The bisphosphonates, calcitonin, gallium and mithramycin all inhibit osteoclastic bone resorption [10]. Bisphosphonates containing nitrogen atoms such as pamidronate, ibandronate and zoledronate are potent than those without, for example, etidronate, clodronate and tiludronate [11]. The former have been associated with transient fever lymphocytopenia, malaise and myalgias [11].

In the case of mild hypercalcaemia (3 mmol/l), fluid repletion and loop diuretic such as frusemide may be sufficient. It is the same in moderate hypercalcaemia (3–3.5 mmol/l), but if there is insufficient reduction, bisphosphonates may be required. In severe cases (>3.5 mmol/l), intravenous administration of bisphosphonates is recommended for initial management of hypercalcaemia followed by oral or repeat IV bisphosphonates to prevent relapse [12]. In very severe cases, calcitonin which is rapidly acting is concurrently administered with bisphosphonates (pamidronate 60–90 over 2 h) as bisphosphonates take about 48 h to lower serum calcium [12]. Bisphosphonates have relatively slow onset of action and may take 1–3 days [12]. The dose of calcitonin is 4 units/Kg subcutaneously or intramuscularly every 12 h, but is not continued indefinitely. Glucocorticoids increase urinary excretion and decrease intestinal calcium absorption and is in granulomatous disease, vitamin D intoxication and in haematological malignancies. Mithramycin because of its toxicity and low efficacy is restricted to patients with hypercalcaemia of malignancy who fail to respond to IV bisphosphonates [11].

Hypocalcaemia

Introduction

Hypocalcaemia has a prevalence of 85% in ICU and 18% of all hospital patients [13, 14]. The causes of hypocalcaemia include hypoalbuminemia, hypomagnesaemia, medication effects, surgical effects, PTH deficiency and vitamin D deficiency [15] and resistance [16]. It is rare for hypocalcaemia to occur from poor dietary intake of calcium. It is more likely to be due to poor intake of vitamin D. Hypocalcaemia occurs in conditions where the plasma protein level is low as in nephrotic syndrome, cirrhosis of liver, malabsorption syndrome and malnutrition. Hypocalcaemia is associated with conditions with low PTH levels (hypoparathyroidism) and with high PTH levels (secondary hyperparathyroidism). The former occurs where there is parathyroid destruction as a result of surgery [15], radiotherapy and infiltration by metastasis. The latter occurs as a result of vitamin D deficiency, vitamin D resistance and PTH resistance (pseudohypoparathyroidism) (Box 2).

Box 2 Causes of Hypocalcaemia

Hypoalbuminaemia
Hypoparathyroidism – postsurgery, idiopathic
Magnesium depletion
Pseudohypothyroidism
Vitamin D deficiency
Medications
Renal failure
Acute pancreatitis
Malignancy
Rhabdomyolysis

Information sources: Cooper and Gittoes [15]

Clinical Manifestations

Hypocalcaemia is often asymptomatic. Acute hypocalcaemia could lead to cardiovascular effects such as syncope, angina and congestive heart failure [16]. Symptoms due to neuromuscular irritability may involve both the smooth and

skeletal muscles and include muscle cramps, numbness and tingling of the extremities. Severe hypocalcaemia may cause tetanic contractions and convulsions and may occur even when the ionized calcium is low without any marked hypocalcaemia. Chvostek sign is elicited by tapping the facial nerve anterior to the tragus of the ear. Graded response will occur with twitching first at the angle of the mouth and then the nose, the eye and the facial muscles. Another sign of latent tetany is Trousseau sign which is elicited by inflating the blood pressure cuff to above the systolic pressure for a couple of minutes resulting in a carpal spasm. This constitutes an extended elbow, flexed wrist, adducted thumb, flexed MCP joints and extension of the interphalangeal joints, and this is positive in about 94% of hypocalcaemic patients [17]. Smooth muscle contractions may give rise to laryngeal stridor, dysphagia, bronchospasm and intestinal and biliary colic. Slowly developing hypocalcaemia may manifest diffuse encephalopathy. Chronic manifestations include cataracts, dry skin, coarse hair and poor dentition. Calcification of the basal ganglia, and in the cerebellum, may occur especially when hypocalcaemia is associated with hypoparathyroid states. Gastrointestinal symptoms include malabsorption with steatorrhoea. The electrocardiogram may show prolongation of the QTc interval due to the lengthening of the ST segment which directly proportional to the degree of hypocalcaemia [18]. T waves are usually normal but can be flattened or inverted [19].

Evaluation

Firstly to ascertain that hypocalcaemia is present, a complete history should include the causes such as neck surgery, medical conditions with hypoalbuminemia (nephrotic syndrome, cirrhosis of the liver, malabsorption), renal disease and medications (phosphates, bisphosphonates, anticonvulsants). Acute pancreatitis, malabsorption, renal failure and drug therapy have to be excluded. The PTH, serum magnesium and vitamin D levels should be evaluated.

Management

Acute Hypocalcaemia

In patients who are symptomatic (tetany, seizures) or at high risk of developing complications, calcium gluconate in 10 ml of 10% diluted with 50–100 ml of 55 dextrose [15] is given intravenously slowly. It is advisable to that ECG monitoring is done because of dysrhythmias can occur if given too rapidly [15]. This can be repeated as necessary, or the calcium gluconate (30–40 ml of 10%) in 1 L of 5% dextrose can be given as an infusion over 12–24 h. The aim of treatment of acute hypocalcaemia is to control the signs and symptoms rather than to normalize the calcium.

Chronic Hypocalcaemia

In chronic hypocalcaemia, oral calcium and vitamin D supplements are usually sufficient. Vitamin D deficiency can be treated with vitamin D2 (ergocalciferol) or D3 (cholecalciferol) [15].

Impact

Hypocalcaemia is often asymptomatic but could present in life-threatening situations. Acute hypocalcaemia could lead to cardiovascular effects such as syncope, angina and congestive heart failure [16]. Hypercalcaemia is a common metabolic disorder in malignant disease. When associated with malignancy, it can be life threatening (Box 3).

Box 3 Key Points. Disorders of Calcium Metabolism

Parathyroid hormone (PTH), vitamin D and ionized calcium and their corresponding receptors and calcium-sensing receptor greatly influence the regulation of calcium.

(*continued*)

Box 3 Key Points. Disorders of Calcium Metabolism (continued)

Malignancy (45%) and hyperparathyroidism(16.5%) [1, 2] are the most common causes of hypercalcaemia [4].

A serum PTH level >4.0 pmol/L and the presence of serum calcium >2.6 mmol/L are indicative of primary hyperparathyroidism.

Several measures are available in the treatment of hypercalcaemia such as fluid repletion normal saline 2–4 L/24 h loop diuretics (IV frusemide 6–12 hourly), bisphosphonates (pamidronate, ibandronate and Zoledronate), calcitonin, mithramycin, gallium, glucocorticoids and dialysis [5].

In patients who are symptomatic (tetany, seizures) or at high risk of developing complications, calcium gluconate in 10 ml of 10% diluted with 50–100 ml of 55 dextrose [13] is given intravenously slowly.

Multiple Choice Questions

1. The following are true regarding calcium metabolism, EXCEPT:
   A. In the kidneys PTH decreases reabsorption of calcium from the distal tubules.
   B. Calcitonin is produced by the thyroid in response to high calcium levels.
   C. Ideally the ionized or free calcium should be determined since this is the active form.
   D. The metabolism of calcium and phosphate are closely related.
2. The following are true of hypercalcaemia, EXCEPT:
   A. Acute hypercalcaemia usually present with gastrointestinal symptom.
   B. In hypercalcaemia the QT interval may be prolonged in some cases and PR interval shortened.
   C. Constipation, dyspepsia and abdominal pain due to pancreatitis are the usual complaints with chronic hypercalcaemia.
   D. Causes of medically induced hypercalcaemia include thiazides, lithium, vitamin A and milk-alkali syndrome.

MCQ Answers

1 = A; 2 = B

Extended Matching Questions

A. Sarcoidosis
B. Malignancy
C. Vitamin excess
D. Milk-alkali syndrome
E. Tertiary hyperparathyroidism
F. Primary hyperparathyroidism
G. Milk-alkali syndrome
H. Hyperthyroidism
I. Familial hypocalciuric hypercalcaemia

The following biochemical findings have raised serum calcium concentration in common. Choose the most likely diagnosis from the list above. Each option can be used only once.

	PTH	Serum P	ALP	Urine Ca+	Urine P	Other
1.	High	Low	Var	High	High	
2.	Var	Low	High	Var	High	PTHrH high
3.	Low	N/High	N/High	High	N	
4.	Low	N/High	N	N	N	
5.	High	N/Low	N	low	N	

N normal, *var* variable, *PTHrH* PTH-related peptide, PTH + parathyroid hormone

EMQ Answers

1 = F; 2 = B; 3 = A; 4 = G; 5 = I

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Part XI

Disorders of the Musculo-skeletal System in the Elderly

It is important to remember that symptomatic musculoskeletal pain may originate from many different sites. A thorough understanding of the functional anatomy of the vertebral column (the spine, intervertebral discs, spinal cord, spinal nerves, muscles, and ligaments) and surrounding soft tissue is highly desirable in regard to assessment and diagnosis of musculoskeletal pain. Part XI provides an overview of the prevalence and mechanisms, evaluation, and clinical management of the common musculoskeletal disorders. It reviews pain arising from the neck, lower back, and the large joints. Pain in the back, shoulders, hips, and knees in the elderly are common complaints encountered by the primary care physician.

The Spine

53

Contents

Abstract

The vertebral column consists of 7 cervical vertebrae, 12 thoracic, 5 lumbar and 5 sacral vertebrae (fused to form the sacrum) and 5 small vertebrae fused to form the coccyx. It radiates pain arising from the neck and low back and the spine. Common clinical syndromes associated with cervical spondylosis are myelopathy and radiculopathy and both syndromes are distinct. The prevalence of low back pain in the elderly is reported to range between 13 and 49%. The aetiology of back pain may be different in older people. As the patients get older, the diagnostic probabilities as to their prevalence change, such as malignancy/neoplasia, compression fractures, spinal stenosis and aortic aneurysms. Spinal stenosis due to hypertrophic degenerative processes and degenerative spondylolisthesis is more common in older people.

Keywords

Neck pain · Low back pain · Cervical spondylosis · Myelopathy · Radiculopathy · Spinal stenosis

Introduction

The vertebral column consists of 7 cervical vertebrae, 12 thoracic, 5 lumbar and the 5 sacral vertebrae (fused to form the sacrum) and 5 small vertebrae fused to form the coccyx [1]. The vertebrae are composed of several elements, the

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_53

vertebral body, *pedicles*, *lamina*, *transverse processes*, *spinous process and superior and inferior articular processes* (the facet joints) [2]. The vertebrae surround the spinal cord. The pedicles and laminae together with the body of the vertebrae are responsible for enclosing the spinal cord. The transverse processes are the sites for the attachment of the muscles and ligaments and in the thoracic spine for the ribs (costo-vertebral and costo-transverse joints). The spinous process is also for the attachment of muscle and ligament. The facet joints are covered with a layer of the cartilage and are surrounded by a joint capsule and bathed in synovial fluid and helps the joints to move smoothly [2]. The shape and orientation of these joints help to guide movements of the spine, namely, flexion and extension, left-right lateral flexion and left and right rotation.

The *intervertebral discs* lie between the vertebral bodies, and each disc consists of an outer annulus fibrosis and an inner nucleus pulposus [1, 2], which is a gel-like elastic substance [2]. The disc is made of proteins called collagen and proteoglycans that attract water. The *spinal cord* extends caudally from the medulla at the foramen magnum and terminates at the lower end of L1 vertebra. The white matter at the cord's periphery contains the ascending and descending tracts of motor and sensory fibres. The anterior (ventral) horns of the 'H'-shaped grey matter receive impulses from the motor cortex via the descending corticospinal tracts; the axons of these cells are efferent fibres of the spinal nerves [3]. From the posterior (dorsal) horn and dorsolateral white matter emanate the dorsal roots that coalesce into two bundles and enter the dorsal root ganglion in the intervertebral foramen and distal to this join the ventral root to form the spinal nerve [4]. Many *internuncial neurons* in the grey matter carry impulses from dorsal to ventral nerve roots from one side to the other and one level of the cord to another [3].

The segments of the cord are functional divisions that correspond approximately to the attachments of the 31 spinal nerve roots [1]. Each spinal nerve emerges from a segment of the spinal cord as anterior (ventral) motor root and a posterior (dorsal) sensory. They unite to form the *spinal nerve*. The *ligaments* consist of (i) the *anterior longitudinal ligament* which is in the anterior surface of the vertebral column and connects the front of the vertebral body to the annulus fibrosis [2], (ii) the *posterior longitudinal ligament* inside the vertebral column connects the posterior part of the vertebral body to the annulus fibrosis [2], (iii) the *ligamentum flavum* connects the laminae of adjunct vertebrae, (iv) the *supraspinous ligament* connects the apices of the spinous processes and (v) the *intervertebral ligament* connects the transverse processes. The ligaments together with the tendons and muscles [2] and intervertebral discs limit spinal movements [2]. The *paraspinal muscles* consist of the long extensors and erector spinal.

Neck Pain

Cervical Spondylosis

Cervical spondylosis results from degenerative changes which embraces the intervertebral discs, facet joints [5], laminal arches, and osteophytosis of the vertebral bodies with ligamentous and segmental instability [6].

Clinical Manifestations

Common clinical syndromes associated with cervical spondylosis are myelopathy and radiculopathy [5] and both syndromes are distinct [6].

i. Myelopathy

Cervical spondylotic myelopathy manifests as pain and stiffness more often in the lower cervical region and in certain positions of the neck. The pain radiates to the base of the neck, shoulders and back. The symptoms include clumsiness and weakness of the hands, leg stiffness with weakness and an unsteady gait [7, 8]. The signs include weakness of the triceps and/or weakness of the intrinsic muscles of the hands with wasting. When the fingers are held extended and adducted if the ulnar digits drift into abduction and flexion within 30–60 s, the

'finger escape sign' is positive, and chronic spondylotic myelopathy between C3 and C5 may be present [9]. The main findings are numbness of the hands with decreased vibration sense and hyperlexia [10]. Though non-specific, Lhermitte sign may be positive, that is, flexion of the neck gives rise to electric shock-like sensations down the back and down both legs. It is seen in posterior column dysfunction. Hoffman's sign is a reflex contraction of the thumb and index finger after nipping the middle finger [11]. It is usually present with corticospinal tract dysfunction but may be present in other generalized hyper-reflexic states. A hyperactive pectoralis muscle reflex is a sign of cord compression at the upper cervical spine (C2, C3–C4) and is elicited by tapping the pectoralis muscle tendon in the deltopectoral groove resulting in adduction and internal rotation of the shoulder [12]. The biceps supinator (C5, C6) may be absent with brisk triceps reflex (C7) indicative of spinal cord compression because of cervical spondylosis at C5–C6 in the spine.

Lower limb weakness is commonly seen with involvement of the iliopsoas followed by the quadriceps muscles. The gait is stiff with progressive paraparesis and paraesthesias and sensory impairment in feet and hands [13]. A 'myelopathic gait' had been described and a hesitant jerking motion may appear [14]. There are several clinical patterns of presentation depending on the predominant neurological findings – subacute cord compression, brachialgia and cord syndrome [3] and central cord syndrome.

ii. Cervical Radiculopathy

It manifests as pain in the neck radiating into either the arm, forearm or hand and often accompanied by numbness.

iii. Regional Pain Syndromes

Chronic occipital headache or cervicogenic headache can be due to upper cervical C2 nerve root lesion or facet joint dysfunction [15, 16]. A chronic suboccipital headache is seen with cervical spondylosis, and it seems likely that occipitoatlantal and atlantoaxial degeneration could cause the pain in those areas [17].

iv. Others

Other manifestations include dysphagia due to large spurs compressing the oesophagus (see viginette at the end of the chapter) [18–20], vertebrobasilar insufficiency and vertigo.

Imaging Studies

Computed tomography and magnetic resonance imaging are used to assess spinal and foraminal stenosis in cervical spondylosis. High-signal intensity lesions can be seen on MRI of spinal cord compression and may indicate myelomalacia and permanent damage [21], and this indicates a poor prognosis [22]. Electrodiagnostic studies may be helpful in assessing continuity of the somatosensory pathways.

Treatment

The only effective treatment for myelopathy is surgical decompression of the cord. The large majority of patients with cervical spondylosis are treated conservatively and surgery reserved for moderate to severe myelopathy or failed medical treatment [23, 24]. In the mild and slowly progressive, immobilization with soft collars or more rigid orthosis like the Philadelphia collar or Minerva body jacket can considerably immobilize the cervical spine. The use of cervical exercises has also been advocated [22]. If progressive, cervical decompression may be required. Reduction of the cord's cross-sectional area by 50–60% is associated with poor operative outcome in cervical spondylotic myelopathy with or without operative intervention [25].

Low Back Pain (Lumbosacral)

The prevalence of low back pain in the elderly is reported to range between 13 and 49% [26] and in another review ranged from 18 to 57% [27]. The aetiology of back pain may be different in older people [28]. In office practice, prevalent estimates

of the causes of low back pain [29–31] were (i) mechanical (97%) – the most common are lumbar strain and sprain followed by degenerative processes of discs and facets and herniated discs, among others and (ii) nonmechanical spinal conditions (about 1%) such as neoplasia, infection and inflammatory arthritis and visceral disease which includes disease of the pelvic organs, renal disease, aortic aneurysm and gastrointestinal disease. As the patients get older, the diagnostic probabilities as to their prevalence change, such as malignancy/neoplasia, compression fractures, spinal stenosis and aortic aneurysms. Spinal stenosis due to hypertrophic degenerative processes and degenerative spondylolisthesis is more common in older people [29]. The older people may be at a greater risk because of the decline in health status with advancing age [28], and poor health is known to be a predictor of back pain [27, 32].

Clinical Manifestations

i. Lumbar Muscles

Lumbar strain occurs after an episode of twisting, lifting or bending with pain and tenderness in the lower lumbar area and often felt in the buttock and upper thigh. This follows tear of muscle fibres or distal ligamentous attachments of the paraspinal muscles at the iliac crest (enthesopathy) or lower lumbar and or upper sacral region.

ii. Piriformis Syndrome

The piriformis muscle lies deep to the gluteal muscles. The pain in the buttocks is worse on sitting, on climbing stairs and on squatting. The piriformis muscle abducts and rotates the thigh laterally. In the supine and relaxed position, the ipsilateral foot is rotated externally, and this is taken as a positive sign of the syndrome [33, 34]. The diagnosis is made on the basis of symptoms and physical examination. It can mimic lumbar radiculopathy, intervertebral discitis, sacroiliitis and sciatica, among others [32]. Treatment consists of exercises, TENS and trigger point injections.

iii. Intervertebral Discs

(a) Degenerative Disc Disease (DDD)

Patients with DDD complain of back pain and may complain of leg pain and numbness.

(b) Herniated Disc

Herniation occurs when the inner nucleus pulposus bulges through the annulus fibrosis causing a protruding disc which may cause irritation of the spinal nerve. Surprisingly, patients with herniated disc may complain only of leg pain with minimal low back pain. Sciatica is the hallmark of nerve root irritation and in 95% of the cases, there is disc protrusion. Depending on the nerve root involved, sciatica is characterized by pain radiating down the posterior or lateral aspect of the leg to the ankle or foot. Weakness may also occur in the areas supplied by that nerve. Movements: flexion at the hip, L1; adduction at the hip, L2; extension at the knee, L3; dorsiflexion of the foot at the ankle, L4; extension of big toe, L5; plantar flexion at the ankle S1 and clawing of the toes, S2. Pain is often accompanied by numbness or tingling and may be worsened by coughing or sneezing. Treatment may include manipulation, physiotherapy, exercise, pelvic/spinal stabilization training, group classes, epidural injections, nerve root blocks and surgery.

(c) Discogenic Disease

Follows injury, infection and tear, the patient usually presents with localized back pain. Recurrent episodes or exacerbations are possible and with treatment is similar to herniated disc problems. In patients with lumbar spinal stenosis or multilevel disc abnormalities, 3D MR myelography may be useful to recognize the site most likely the cause for the pathology [35]. Infectious discitis is primary infection of the intervertebral disc and adjoining vertebrae. There do seem to be any difference in the treatment and outcome between discitis and other spinal infections [36].

The Spine

(a) Spinal Stenosis

Spinal stenosis is encroachment of bony or soft tissue structures in the spine on one or more of the neural elements giving rise to symptoms. Patients with spinal stenosis usually present with back pain, initiated by walking [37], bilateral sciatica, neurogenic claudication and pain with hyperextension and with standing and relief with bending forwards at the waist or sitting [36] and by lying down. Extension of the spine causes increase in pain [38, 39]. Central canal stenosis can cause a variety of symptoms depending on its location and typically it causes neurogenic claudication [40]. Unlike vascular claudication, pain is relieved with lumbar flexion [37]. The differential diagnosis in the elderly includes aortic aneurysms, compression fractures and cancer [29]. Treatment includes flexion-based exercises, muscle strengthening, stabilization, epidural injections and surgery.

(b) Osteoporotic Compression Fractures

Patients could present with acute pain following severe flexion-compression force. Spontaneous vertebrae collapse is seen in elderly people with osteoporosis or on long-term glucocorticoids (see ▶ Chap. 44, "Osteomalacia").

(c) Neoplasia

The pain is worse on lying supine and by activity. With spinal metastases, pain precedes weakness or sensory symptoms by an average of 3 months. About 30% of the vertebral lesions are asymptomatic [41]. Since early diagnosis and treatment determine the functional result, middle aged or older patients with persistent pain for more than a month should have an imaging study of the spine, preferably an MRI. This is mandatory if there is known systemic cancer.

(d) Spondylolisthesis

Spondylolisthesis is the forward subluxation of a vertebral body. The low back pain is caused by strain on the ligaments and intervertebral joints. Management is dependent on the severity and progression of the listhesis and may include non-surgical physical therapy, medications and steroid injections and surgery which do not respond after a trial of medical treatment [42].

(e) Facet Syndrome

Facet syndrome is a type of arthritis of the facet joints. Studies on low back pain have shown that the prevalence of facet joint involvement is approximately 15–45%, and the age-related prevalence of facet neck pain is similar among all age groups [43]. Regardless of clinical severity, more than 90% demonstrate degenerative disc and facet pathology in older adults [44]. There is pain on hyperextension with relief on lumbar flexion, decrease in range of movement and local facet tenderness [45, 46]. There is degeneration of the facet joints with 'jamming' causing pinching of the sensitive meniscoid tabs within the joint. It may also cause pinching of the spinal nerves as they exit. It often presents with pain, numbness and tingling, and most of these symptoms may be attributed to pain of discogenic origin [46]. Pain severity among those with chronic low back pain was not associated with radiographic severity of disc and facet disease [44].

Diagnosis

History

i. Basic features of pain such as location, onset and radiation
ii. History of recent injury
iii. History current or past history of cancer
iv. Symptoms of serious underlying disease – fever, concurrent infection, progressive neurological deficits, saddle back anaesthesia, bladder dysfunction and recent lumbar puncture
v. Aggravating and alleviating factors:
   - Morning stiffness of the back relieved by activity (inflammatory conditions)

     Onset or worsening of symptoms on walking or standing and relief by bending or sitting down (spinal stenosis)

- Worsening with sitting, driving or lifting (disc herniation)
- Mid back pain worse on lying supine or activity (malignancy)

vi. Associated symptoms include fever, neurological deficits such as truncal or saddle back anaesthesia, difficulty climbing stairs and altered bowel and bladder function including urinary and/or faecal incontinence
vii. Effect of pain on daily activities
viii. Emotional and social stresses

Examination

Examination of the spine encompasses observation for deformity, listing, loss of normal curvature and poor posturing. Assessment of the amount and quality of active and passive range of movement is essential. Muscle and joint palpation is useful for localizing nocigenic structures. A complete neurological examination is always preferred when nerve involvement is suspected or when spinal pain, pins and needles and numbness extend beyond the point of the shoulder or beyond the buttock. Straight leg raising test can assist to differentiate between hamstring tightness and sciatica and aims to sensitize the neural structures without increasing tension on the lumbar spine or hamstrings. A search for systemic cancer is also advisable in the older age group. The clinical examination of the patient with back pain includes imaging and can delineate disc herniation and disc degeneration and can suggest the presence of discogenic pain [47]. Central canal, neuroforaminal stenosis and lateral recess stenosis can be readily recognized by imaging with MRI, CT or CT myelography [47].

Impact

Chronic back pain is common in the elderly, but because of the age-related co-morbidities in the elderly, the exact impact of chronic low back pain is not known [48]. However, with the population expecting to survive until their eighth and ninth decade, the impact of chronic back pain will be substantial [28]. In older adults, musculoskeletal pain is frequently under-reported and poorly treated [49] more so at the end of life [50]. Although the prevalence of pain in different parts of the body decreases with age, the degree of pain disrupting everyday life continues to increase with age [51]. Neck pain and low back pain are common musculoskeletal afflictions in the elderly population. Pain can be either chronic or intermittent. Spinal pain is a frequent complaint in older persons and is responsible for functional limitations [43]. The elderly are particularly susceptible to the negative aspects of pain and pain-associated events [52]. There is a reduced capacity in the functional reserve of the pain system [52], and there are physiological, pathological and psychological reasons for altered pain sensibility with ageing [53]. The elderly present with greater physical and less psychosocial impairment compared to younger adults [54]. Chronic pain has the capacity to put at risk the functional independence of older adults [55]. Older adults with low back pain have longer symptom duration and are more disabled and less depressed compared to younger adults [56]. In a study of a large cohort of well-functioning community-dwelling adults aged 72–75, the frequency and intensity of low back pain were associated with perceived difficulty in performing important functional tasks but not with observed physical performance [57]. Not only does chronic low back pain reduce physical performance, it increases fear avoidance behaviour in elderly adults [58]. In the 70 years and over, depression is notably associated with disabling back pain [58]. Back pain is associated with increased disability and healthcare costs [55, 59]. Billions of dollars are spent each year in the belief of relieving neck and back pain and most of which are towards pain medication, surgery and diagnostic imaging (Box 1).

Box 1 Key points: Pain in the back (neck and low back)

Cervical

Common causes are cervical spondylosis, cervical dysfunction, traumatic stress or spasm, disc prolapse and fibromyalgia.

(*continued*)

Box 1 Key points: Pain in the back (neck and low back) (continued)

Common clinical syndromes associated with cervical spondylosis are myelopathy and radiculopathy [5]; both syndromes are distinct [6] and regional pain syndromes.

Chronic occipital headache or cervicogenic headache can be due to upper cervical C2 nerve root lesion or facet joint dysfunction [15, 16] and a chronic suboccipital headache [17].

The large majority of patients with cervical spondylosis are treated conservatively and surgery is reserved for moderate to severe myelopathy or failed medical treatment [23, 24].

Lumbosacral

In office practice, prevalent estimates of the causes of low back pain [29–31] were (i) mechanical (97%) – most common are lumbar strain and sprain followed by degenerative processes of discs and facets and herniated discs, among others.

As patients get older, the prevalence changes to malignancy/neoplasm, compression fracture, spinal stenosis and aortic aneurysms.

Patients past middle age with bony lesion should include metastases in the differential diagnosis.

Multiple Choice Questions

1. A 75-year-old man is seen with a history of a fall and inability to walk. X-ray revealed a fracture of the neck of the femur (cervical). Each of the following statements is true, except:
   A. The leg was held in flexion, adducted and internally rotated.
   B. The greater trochanter was elevated on the injured side.
   C. All movements were extremely painful.
   D. Extreme tenderness on palpation.
2. A 70-year-old is seen following a motor vehicle accident. He was a passenger in the front seat. X-ray showed a posterior dislocation of the hip. Each of the following signs is true, except:
   A. Leg is internally rotated, flexed and adducted at the hip.
   B. The affected leg was shortened.
   C. All movements were painful.
   D. The head of the femur was felt in the groin.
3. A 73-year-old man presented with low back pain for 3–4 months. The serum alkaline phosphatase was 320 (rr 35–110) U/L, calcium 2.4 mmol/l (corrected 2.32 mmol/l), phosphate 3.2, total proteins 70 g/l(rr 60–80) and albumin 41 g/l (rr 34–45). A bone scan demonstrated several focal areas of increased uptake ('hot spots') in the vertebrae, pelvis and ribs. Which of the following is most likely the cause?
   A. Paget's disease
   B. Multiple myeloma
   C. Metastatic prostate cancer
   D. Hyperparathyroidism
4. A 65-year-old man developed severe low back pain radiating down the left leg on attempting to lift a heavy object. Plain X-ray showed a narrowing of the disc space L4/L5. Which of the following findings is incorrect?
   A. Straight leg raising test – limited to 45 in the left leg.
   B. Knee jerks were exaggerate.
   C. Weakness of dorsiflexion of the big toe.
   D. Diminution of sensation to touch and pain on the lateral aspect of the leg and dorsum of the foot.
5. A 75-year-old man with chronic low back pain has spinal stenosis. Each of the following symptoms is true, except:
   A. Relieved by hyperextension and standing
   B. Intermittent claudication
   C. Pain in both buttocks radiating down the legs
   D. Pain relieved by bending forwards at the waist

MCQ Answers

1 = A; 2 = D; 3 = C; 4 = B; 5 = A

Case Study of Dysphagia

A 69-year-old man presented with difficulty in swallowing over a period of several months with pain made worse on moving the neck. There was no history of trauma. The neck movements were restricted in all directions on examination. Radiological examination of the cervical spine revealed narrowing of the disc spaces of the entire cervical spine, spur formation and posterior osteophyte changes consistent with cervical spondylosis. There was marked anterior beaking of C5 and C6 vertebrae (Fig. 1).

Discussion

Cervical spondylosis of some degree on the basis of plain radiographs is seen in the adult population, 50% over the age of 50 years and 70% over the age of 65 years. Most patients are symptom-free. Compression of the oesophagus by osteophytes is uncommon to a degree giving rise to dysphagia. Mosher in 1926 [60] described two patients with exostosis of the cervical vertebrae giving rise to dysphagia. There have been reports of moderate degenerative disease of C4–C5 and C5–C6 with moderate encroachment upon C4–C5 by cervical osteophytes presenting with dysphagia of gradual onset, and videofluoroscopy showed spurs pressing on the postpharyngeal wall. The patient has had trauma to his neck [61].

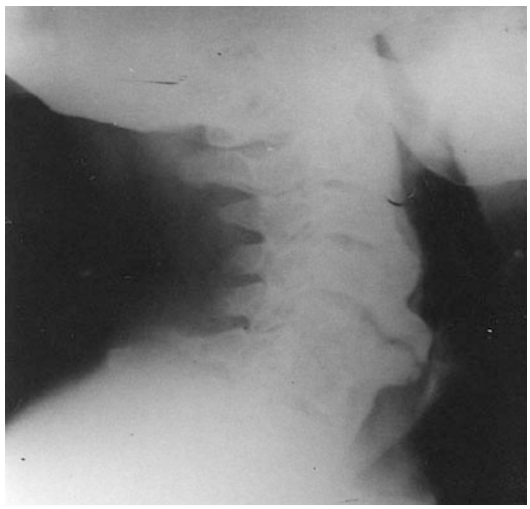

Fig. 1 Shows narrowing of the disc spaces and marked anterior breaking of C_5 and C_6 vertebrae

The changes seen in our patient were unlike that seen in diffuse idiopathic skeletal hyperostosis (DISH). This is a rare ossifying diathesis of unknown aetiology and characterized by exuberant bone outgrowths in axial and extra-axial sites and seen along the anterolateral margins of the cervical and thoracic vertebrae [62]. The intervertebral discs are usually well preserved unlike that seen in our patient.

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Large Joints

54

Contents

Abstract

Shoulder pain is usually due to injury to one of the structures comprising the joint. The hip joint is a ball-and-socket joint and is formed by the articulation of the rounded head of the femur and the cup-like acetabulum formed by the union of three pelvic bones. A good history and physical examination usually determine the cause of the shoulder, hip and knee pain.

Keywords

Shoulder pain · Hip pain · Knee pain · Rotator cuff tears/strain · Trendelenburg gait

Shoulder

Introduction

Shoulder pain is usually due to injury to one of the structures comprising the joint. Muscles: The *trapezius*, *deltoid and pectoralis muscles* are around the joint. Wrapping around the humerus and to hold it in the glenoid fossa are the *rotator cuff muscles* which originate from the scapula. Originating from the spine of the scapula is the *supraspinatus muscle* which runs under the acromion and over the humerus to attach on the lateral

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_54

humerus. It assists with external movement and is the muscle that is torn in the rotator cuff tears and commonly gets impinged between the acromion and the humerus. The *subscapularis* from the underside of the scapula attaches anteriorly to the lesser tuberosity of the humerus. It rotates the arm internally. The *infraspinatus* and *teres minor* arise from the lower scapula attaching to the posterior humerus to the middle and inferior aspects of the greater tuberosity, respectively. They externally rotate the arm. The rotator cuff tendons fuse with the underlying capsule of the shoulder and stabilise the humeral head. Movements: *abduction* (deltoid and supraspinatus (0–170 °)), *flexion* (pectoralis major, biceps and deltoid (0–160 °)), *internal rotation* (subscapularis and teres minor (0–70 °)) and *external rotation* (infraspinatus and teres major (0–70 °)).The *glenohumeral joint* is made up of the glenoid fossa, the humeral head, the joint capsule and the labral cartilage which helps to hold the humerus head in place.

Causes

The common causes of shoulder pain are shown in Table 1.

Evaluation

A good history and physical examination usually determine the cause of the shoulder pain. The examiner should compare both sides both with the patient standing relaxed and during abduction of the arms to above the head. Muscle wasting should be noted. Palpation should be performed to elicit any tenderness.

Movements are tested: Abduction is usually tested actively. Rupture of the supraspinatus tendon prevents initiation of abduction. The 'painful arc' is through the mid range of abduction. The deltoid completes the movement. Flexion is arm swung forwards and extension swung backwards. The height up the back which can be reached is internal rotation and it combines glenohumeral and scapular movement. The external movement is pure glenohumeral movement. In rotator cuff tendon tears, the supraspinatus or infraspinatus tendons lose their normal integrity [3]. Significant movements of abduction and rotation are lost in adhesive capsulitis [3] with increased pain on extreme of movement [5, 6].

Testing for the rotator cuff muscles includes (i) internal rotation (subscapularis), (ii) external rotation (teres minor and infraspinatus) and (iii) abduction with thumbs down and arm parallel to the ground (supraspinatus). The impingement test is done with the arm 90 degrees forwards and flexed parallel to the ground and gently internally rotated [4]. Pain during provocative shoulder testing indicates a rotator cuff dysfunction but may not be limited to the individual muscle with isolated testing indicates a positive test (Table 2).

Table 1 Causes of shoulder pain

	Acute	Chronic
Muscles	Biceps tear	Degenerative tear and impingement of rotator cuff
	Pectoralis major tear	
	Rotator cuff tears/strain	
Glenohumeral joint	Dislocations	Arthritis – OA, RA, Milwaukee
	Subluxations	Frozen shoulder
	Labral tears	Chronic labral tears
Bones and acromio clavicular joint (AC)	Fractures, clavicle Humerus, scapular	AC joint capsulitis
Tendons	Acute calcific tendonitis	Posterior cuff tears
Bursae	Acute calcific bursitis	Degenerative bursitis
Capsules	Adhesive capsulitis	Degenerative capsulitis

Information sources: Hermoso and Calvo [1], Karnath [2], Anderson [3] and Brookside Associates [4]

Table 2 Differential diagnosis of shoulder pain

Condition	Cause	Nature pain	Findings
Bicipital tendonitis	Heavy lifting, repetitive movements	Pain/aching anterior shoulder and upper arm	Anterior flexion of shoulder against resistance with arm outstretched in supination, tenderness in groove
Rotator cuff syndromes (complete and incomplete tears)			
Tears	Overuse esp. arms over the head	Pain in the shoulder	Abduction of fully internally rotated humerus; reaching forwards – hand shake; pain when the arm is raised weakness
		Night pain	
	Weight lifting		
Impingement	Rotator cuff between the acromion and greater tuberosity	Pain with overhead reaching and positioning	Abduction or elevation impingement test positive
Tendonitis	Calcific	May cause acute pain over outer deltoid	Focal tenderness, acute pain with motion aggravated by pushing, pulling, reaching, lifting and positioning the arm above shoulder level
Adhesive capsulitis (to frozen shoulder)	Trauma prolonged immobilisation	Diffuse tenderness around the shoulder and stiffness	Decreased range of motion, (often with pain) for active and passive movements
Subacromial bursitis	Repetitive use or trauma	Pain	Tenderness over bursa

Information sources: Karnath [2], Anderson [3], Brookside Associates [4], Self [5], Iannotti and Kwon [6], Stevenson and Tonjian [7]

Hip

Introduction

The hip joint is a ball-and-socket joint and is formed by the articulation of the rounded head of the femur and the cup-like acetabulum formed by the union of three pelvic bones. Hyaline cartilage lines the articular surfaces. A fibrocartilaginous rim called the labrum increases the depth of the acetabulum and grips the head of the femur and stabilises the joint. The entire head of the femur is covered by the hyaline cartilage but for a small area called the fovea which is the site for an attachment for the intracapsular ligament (ligamentum teres). Enclosing the joint is a loose fibrous capsule (circular and longitudinal fibres) which is attached proximally to the acetabulum beyond the acetabular labrum. It covers the head and neck of the femur like a sleeve and attaches to the base of the neck. The hip joint is reinforced by three ligaments, iliofemoral (from the pelvis to the femur), ischiofemoral (ischium to the acetabular rim) and pubofemoral (pubis to femur). Movements*: flexion* (iliopsoas, sartorius, tensor fascia and rectus femoris), *extension* (gluteus maximus, hamstrings), *adduction* (adductor magnus, longus and brevis), *abduction* (gluteus medius and minimus) and *rotation* (obturator internus and externus, quadratus femoris, gemellus superior and inferior).

Causes of Hip Pain

The causes and differential diagnosis are shown in Box 1 and Tables 3, 4 and 5, respectively. Hip pain can be categorised as anterior, lateral or posterior hip pain [8]. The common causes in the elderly are osteoarthritis, osteonecrosis, trochanteric bursitis, malignancy, osteoporosis, radiculopathy, labral tears and overuse.

Box 1 Causes of Hip Pain

Osteoarthritis
- Septic arthritis
- Avascular necrosis
- Secondary to Paget's disease
- Labral tears and loose bodies
- Ligamentum teres rupture

(*continued*)

Box 1 Causes of Hip Pain (continued)
Femoroacetabular impingement
Hip fracture and dislocations
Osteonecrosis
Trochanteric bursitis
Meralgia paraesthetica
Iliotibial band syndrome
Entrapment of lateral femoral
Cutaneous nerve
Sciatic nerve irritation
Piriformis syndrome
Snapping hip syndrome
Information sources: Karnath [9], DeAngelis and Busconi [10], Tibor and Sekiya [11]

Evaluation

A good history followed by physical examination usually determines the cause of the hip pain [12, 13]. Trendelenburg gait is a good indicator of intraarticular as well as in patients with extra-articular problems, and Trendelenburg test is used to evaluate deficient or painful abductor muscles [10].

Radiography has been recommended when the pain is more than 4 weeks in duration [12, 13]. Most intraarticular hip disorders can be diagnosed with plain radiographs [10]. Fractures can be missed with hip radiography subsequently diagnosed when evaluated with CT or MRI [14]. Advancements in MRI have facilitated the diagnosis of soft tissue causes of hip pain [10, 11] and subtle degenerative changes [10]. The patients are now being evaluated for hip pain with advancements in hip arthroscopy [11], and the hip pain that can be attended to are loose bodies, labial tears, chondral damage [10, 11], tears of ligamentum teres and femoroacetabular impingement [11].

Knee

Introduction

It is synovial hinge-type joint. The articular surfaces between the condyles of the femur and tibia are covered with hyaline cartilage and are

Table 3 Differential diagnosis of lateral hip pain

Condition	Cause	Findings
Trochanteric bursitis	Lateral hip on walking, rolling onto side	Tenderness on palpation of the bursa, pain on abduction of affected leg when lying on unaffected side
Meralgia paraesthetica	Lateral femoral Cutaneous nerve Compressed, pinched under inguinal ligament	Lateral hip and worsened by exercise, pain, paraesthesia – anterolateral thigh
Iliotibial band syndrome	Lateral thigh	Snapping sensation over greater trochanter on flexion and extension
		Abduction of affected leg and knee flexed to 90 degrees when the patient lies on the unaffected side

Information sources: Karnath [9] and Ivin [18; 19].

Table 4 Differential diagnosis of posterior hip pain

Condition	Cause	Findings
Sciatica	Compression at sciatic notch	Ache in the buttock
Nerve root irritation	Herniated intervertebral discs	Radiating down posterior thigh Low back pain radiating down posterior thigh Straight leg raising test positive
Piriformis syndrome	Sciatic nerve irritated by piriformis muscle	Pain on sitting, squatting and climbing stairs

Information sources: Karnath [9] and Boyajian-O'Neill et al. [20]

Table 5 Differential diagnosis of anterior hip pain

Condition	Cause	Findings
Osteoarthritis	Degenerative	External and internal rotation in the sitting position produces pain, limitation of motion
Stress fracture of femoral neck	Osteoporosis History of fall	Pain on internal rotation and hopping X-ray may show a hairline fracture. Bone scanning is a study of choice, but MRI though has similar sensitivity is more specific for stress fractures
Avascular necrosis	Traumatic fracture, corticosteroids, alcohol abuse, caisson disease, gout sickle cell disease, idiopathic	Pain and limitation of hip movement, passive movements also restricted. Usually bilateral. Fiscat's (1985) Four stages (1) normal X-ray (2) shows remodelling, sclerotic and cystic areas, (3) flattening of the femoral head and (4) joint space narrowed and secondary degenerative changes in the acetabulum
Acetabular labral tears	May or may not be associated with injury	Groin pain and anterior thigh
		Episodes of deep clicking

Information sources: Karnath [9], O'Kane [15], McCarthy et al. [16] and Fiscat [17]

separated by the medial and lateral menisci cushioning the joint. Surrounding the joint is the capsule which is lined on its inner aspect by the synovial membrane that secretes fluid to lubricate the joint. Stabilisation of the joint is provided by the ligaments and to a lesser extent the capsule. The ligaments are tense in all positions and increase in tension in extremes of flexion and extension. The medial and lateral collateral ligaments (MCL, LCL) serve to stabilise the medial and lateral aspects of the joint and serve to restrain rotation. Two internal ligaments, the anterior and posterior cruciate ligaments (ACL, PCL), provide static support. ACL prevents anterior displacement of the tibia on the femur and the PCL prevents posterior transition of the tibia on the femur. Both ligaments tend to reduce rotation of the femur on the tibia. The bursae decrease friction over the tendons and bones. The suprapatellar bursa lies between the deep surface of the quadriceps muscles in the distal part of the femur and communicates with the joint capsule. The infrapatellar bursa is between the skin and the patella ligament, and the prepatellar bursa is between the superficial surface of the patella and the skin. Movements: *extension* (quadriceps muscle – vastus medialis, vastus lateralis, vastus intermedius and rectus femoris – inserted on the proximal edge of the patella and transfers action via the patella tendon to the tibia), *flexion* (hamstring group of muscles), *external rotation* (biceps femoris) and *internal rotation* (sartorius and gracilis also participate in knee flexion).

Knee pain may be categorised as to the location of the pain. Anterior knee pain in the elderly is most commonly due to osteoarthritis of the knee which is caused by breakdown of the articular cartilage causing painful grating of the patella-femoral joint [21]. Posterior knee pain is caused by ligamentous injury, meniscal injury, bone injury, nerve injury, tendon and muscle injury, knee cysts and bursal injury [22]. Medial knee pain results from involvement of the medial collateral ligament, medial cartilage and meniscal tear and arthritis. Lateral knee pain can be due to iliotibial band syndrome, injury to the lateral collateral ligament and lateral meniscal tear. Osteoarthritis is one of the five leading causes of disability in elderly men and women; a relatively common cause of pain in the knee in older women is osteonecrosis [23]. Knee pain in the elderly could be acute, chronic and acute on chronic. Table 6 shows some of the causes of knee pain.

Evaluation

A history followed by physical examination usually determines the cause of the knee

Table 6 Some causes of knee pain in the elderly

Condition	Cause	Symptoms	Diagnosis
I. Acute			
i. Ligamentous injuries			
MCL	Pushing medially and stretching the inner at the ligament knee	Feeling a pop or locking, pain along the inner side of the knee	Patient lies supine, leg hanging off the table
			Apply stress against the knee pulling laterally at the ankle or foot, pain or gap in the medial joint (valgus stress)
LCL	Injury that pushes the knee from inside	Pain or tenderness along outer side of the knee	Pushing laterally at the ankle while pulling medially at the knee (varus stress)
ACL	Falls, collapses, sudden stopping or changing direction	Popping sound, buckling on standing	Patient lies supine, knee flexed at 90 ° and foot stabilised, attempt to slide the tibia anteriorly detectable motion is +ve
PCL	Direct impact, e.g. knee impact on dashboard in car accidents	Popping sensation in the knee	Similar to above except
		Pain on walking	Attempt to slide the tibia posteriorly
ii. Meniscal injuries (common in adults and in the elderly more than the average population)			
	Twisting or rotating of upper leg while the foot is firmly on the ground	Pain on straightening	Flexed knee is slowly extended with the tibia
			Held in internal or external rotation[a] – pain
			Pop or click is heard on palpation along medial joint line

Information sources: Karnath [9] and Budoff and Nirschi [24]
MCL medial collateral ligament, *LCL* lateral collateral ligament, *ACL* anterior cruciate ligament, *PCL* posterior cruciate ligament
aMcMurray's test

pain. The history should include the nature of the pain, mechanical symptoms such as locking and popping and the mechanism of injury [25]. When there is a suspicion of a ligamentous or meniscal injury, physical examination is moderately sensitive but more specific [26]. X-rays should be done when the patient is 55 years or older or there is difficulty in bending the knee to 90 degrees or inability to bear weight and/or isolated patella tenderness or tenderness at the head of the fibula [25]. MRI is more sensitive for ligamentous and meniscal damage but less specific compared to physical examination [26]. Box 2 shows acute states requiring urgent intervention or referral.

Box 2 Acute exacerbation requiring urgent intervention or referral:

i. Sepsis (fever)
ii. Gout/pseudogout/haemarthrosis (erythema, warmth, swelling – effusion)

Box 2 Acute exacerbation requiring urgent intervention or referral: (continued)

iii. Avascular necrosis(severe pain predominantly at night)
iv. Baker's cyst especially with rupture
v. Inflammatory arthropathy
vi. Meniscal tear
vii. Osteochondral bodies
viii. Prepatellar bursitis

Information sources: NHS [27] and Prevention, Care Recovery [28]

Acute exacerbation requiring urgent intervention or referral is shown in Box 3.

Impact

The musculoskeletal system can be affected in many ways. The joints can be involved and the

cause of the damage can vary. The elderly are particularly susceptible to the negative aspects of pain and pain-associated events [29]. Pain can affect every aspect of life. The elderly present with greater physical and less psychosocial impairment compared to younger adults [30]. Chronic pain has the capacity to put at risk the functional independence of older adults [31].

Box 3 Key Points: Large Joints

Shoulder pain is usually due to injury to one of the structures comprising the joint.

A good history and physical examination usually determine the cause of the shoulder pain.

Hip pain can be categorised as anterior, lateral or posterior hip pain.

The common causes in the elderly are osteoarthritis, osteonecrosis, trochanteric bursitis, malignancy, osteoporosis, radiculopathy, labral tears and overuse.

Trendelenburg gait is a good indicator of intraarticular as well as in patients with extraarticular problems, and Trendelenburg test is used to evaluate deficient or painful abductor muscles [10].

The history should include the nature of the knee pain, mechanical symptoms such as locking and popping and the mechanism of injury.

Multiple Choice Questions

1. A 67-year-old woman presented with pain on walking. X-ray of the knee showed moderate diminution of joint space and osteophytes. Each of the symptoms is true, *except*:
   A. Morning stiffness
   B. Postexercise gelling
   C. Crepitus
   D. Full range of movements and function
2. A 64-year-old woman had a fall and presented with swelling of the knee. Ultrasound demonstrated a medial meniscal tear. Each of the signs is true *except*:
   A. Unable to straighten knee
   B. Recurring locking of the knee
   C. Pain on abduction of the knee
   D. Tenderness medial to the patella

MCQ Answers

1 = D; 2 = C

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Part XII

Arthritides in the Elderly

Part XII provides information on the arthritides – rheumatoid arthritis (RA), osteoarthritis (OA), polymyalgia rheumatica (PMR), crystal-induced arthritis, psoriatic arthritis, and spondyloarthropathy that are common in the elderly. The review provides an overview of the prevalence and mechanisms with the main focus on age at onset. One-third of the patients with rheumatoid arthritis have their first symptom after the age of 60 years. In the elderly, RA takes two forms: (i) continuing into old age with earlier onset and (ii) the elderly onset (EORA). Clinical emphasis is placed on these differences, for failure to recognize them may result in delay in diagnosis and treatment. About 15% of the patients with PMR develop giant cell arteritis (GCA) and every patient with PMA should be considered a risk for GCA. Elderly onset psoriatic arthritis (EOPsA) has a more severe onset and more destructive outcome than in younger subjects. The clinical spectrum of PsA can range from typical features of spondyloarthropathy to pseudo-rheumatoid disease. In the diagnosis of osteoarthritis those with erosive changes, absence of wrist and MCP joint should exclude RA and further confirmed by negative RF and anti-CCP antibodies. In the pathogenesis of OA there has been considerable interest in the role of bone and bone marrow lesions (BML). They are an important source of OA symptoms and are implicated in the causation and pathogenesis of the disease. Late-onset peripheral spondyloarthropathy (LOPS) is characterized by severe disease, markedly raised inflammatory markers, oligoarthritis and edema of the extremities, and HLA- B27 is positive. Gout occurs in two forms: classical gout presenting in middle age and elderly onset gout (EOG) and because of its atypical presentation is often seen to be a separate entity. Health-related quality of life (QOL) in patients with rheumatoid arthritis is significantly impaired as a result of impaired physical function, pain, and fatigue associated with the disease. Arthritis impacts health, threatens the independence, and has large economic and health costs. It causes disability that results being house bound and is a risk for institutionalization. It interferes with basic activities such as self care, walking, and stooping. Persistent pain, fatigue, and psychological stress are problems from the patient's perspective. Patients with PsA have an increased risk of developing cardiovascular disease and metabolic syndrome.

Rheumatoid Arthritis

55

Contents

Abstract

The review provides an overview of the prevalence and mechanisms, with the main focus on age at onset. One-third of the patients with rheumatoid arthritis have their first symptom after the age of 60 years. In the elderly, RA takes two forms: (i) continuing into old age with younger-onset RA (YORA) and (ii) elderly-onset RA (EORA). Clinical emphasis is placed on these differences, for failure to recognise them may result in delay in diagnosis and treatment.

Keywords

Rheumatoid arthritis · Elderly-onset rheumatoid arthritis (EORA) · Young-onset rheumatoid arthritis (YORA) · Anti-CCP (anti-cyclic citrullinated peptide antibody) · Biological DMARDs (bDMARDs)

Introduction

The history of the origin of arthritis is a subject of continuing debate. Skeletal remains dating back to 4,500 BC had shown signs of rheumatoid arthritis among Native Americans of Tennessee [1]. More recently, evidence of rheumatoid arthritis (RA) was found in palaeopathological samples showing ulnar deviation and damage to the index finger [2]. According to Short [3], there is no conclusive evidence of RA occurring in ancient times and refuted the ancient origin hypothesis and postulated that RA is a disease of recent origin. The first description of the RA was by a French physician, Augustin Jacob Landré-Beauvais which appeared in 1800 [4–7]. Alfred Garrod distinguished gout from other forms of arthritis [5], and it was his son Archibald Garrod who coined the term 'rheumatoid arthritis'

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_60

[5]. RA was said to be at least uncommon before the nineteenth century despite extensive investigations [8]. This may have been due to the estimated average life expectancy being under 30 years when RA was first described in the year 1800 [9] for RA generally manifests between the ages of 30 and 65 [10].

The incidence of rheumatoid arthritis has increased and affects 1% of adults worldwide [11, 12], and the annual incidence in the United States is about 70 per 100,000 annually [13]. Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease characterised by uncontrolled non-suppurative proliferative synovitis and an array of systemic effects [14]. There is a geographical variability [15] in the occurrence of RA among countries and regions [16]. Among the white population in Europe and America, the prevalence is about 1% and the incidence is 0.3% with lower rates in African and Asian populations [15]. The prevalence is between 0.5 and 1% of adult population worldwide with higher prevalence in women and the elderly [17]. The incidence and prevalence increase with age [18], and about a third of the patients have their first symptom after the age of 60 years [19]. The peak onset is in the third to fifth decade of life with an average age of onset of 42 ± 10 years [20]. There is another smaller peak in the sixth decade of life (68 ± 4.6 years) [21]. The prevalence increases with advancing years [21] and continues to rise to the ninth decade of life [22]. In another study, the prevalence of RA was highest (2.4%) in those aged 65 years and had a tendency to decline with age, and no RA was seen after the age of 80 years and over [23]. The prevalence in persons 60 years of age and over in the United States was approximately 2% [24]. Since the 1950s, the prevalence of RA may have fallen in women but not in men [25]. In countries with high rates of RA, incidence and prevalence showed a decreasing trend [16].

Elderly-onset rheumatoid arthritis (EORA) after the age of 60 [26] is distinctly different from the young-onset rheumatoid arthritis (YORA) [27, 28] clinically [29], genetically [21], prognostically and therapeutically [30]. In the elderly, it can take two forms, (i) continuing into old age with an 'earlier' onset and (ii) the elderly onset at the age of 60 years or over. Classical RA is twice as common in women than in men but in EORA there is a more balanced gender distribution [31].

RA is a system disease and the pathogenesis involves genetics [4], environmental factors [14] and autoimmunity [32, 33]. RA is associated with histocompatibility complex antigens, HLA-DR4 and the expression of genes PTPN22 and PAD14 and, together with family studies, confirms the genetic basis in the disease [33, 34]. HLA contribution to hereditability is estimated to be 11–37 [32]. The family history is important [35], the prevalence rate in first-degree relative is 2–3%, and the concordance rates in monozygotic twins for RA are between 15 and 20% [36, 37].

Joint damage begins at the synovial membrane [14] with swelling and synovial proliferation with pannus formation followed by cartilage and bone destruction [38]. Enzymes secreted by the synoviocytes and chondrocytes degrade the cartilage [14]. Pro-inflammatory cytokines play an important role [39, 40] in maintaining chronicity mediating tissue damage [41]. Cytokines especially IL-6, IL-1 and TNF-alpha [14, 42, 43] and chemokines are elaborated, propagate inflammation, recruit leucocytes to the synovium and cause synovial inflammation [14]. It has been demonstrated that IL-1 in the synovial fluid and the disease activity correlate with IL-1 concentrations in the plasma [44]. High levels of IL-1 are found in patients with erosive RA [45] and are the key indicator of synovial inflammation and pannus formation [46] to the destruction of the bone and cartilage [45, 47, 48] (Fig. 1). T cells, B cells and pro-inflammatory cytokines promote development of systemic effects such as chronic anaemia, osteoporosis and cardiovascular disease [14]. EORA patients have different patterns of pro-inflammatory cytokines compared to YORA patients [49]. In RA, elevated bone resorption by osteoclasts results from the imbalance of osteoblast-osteoclast axis initiated by inflammatory processes resulting in bone erosion [50]. Bone damage (erosions) in RA joints involves two pathways, the receptor activator of the nuclear factor kB ligand (RANKL) which is involved in osteoclast formation and the Wnt pathway in the differentiation of osteoblasts from mesenchymal lineage

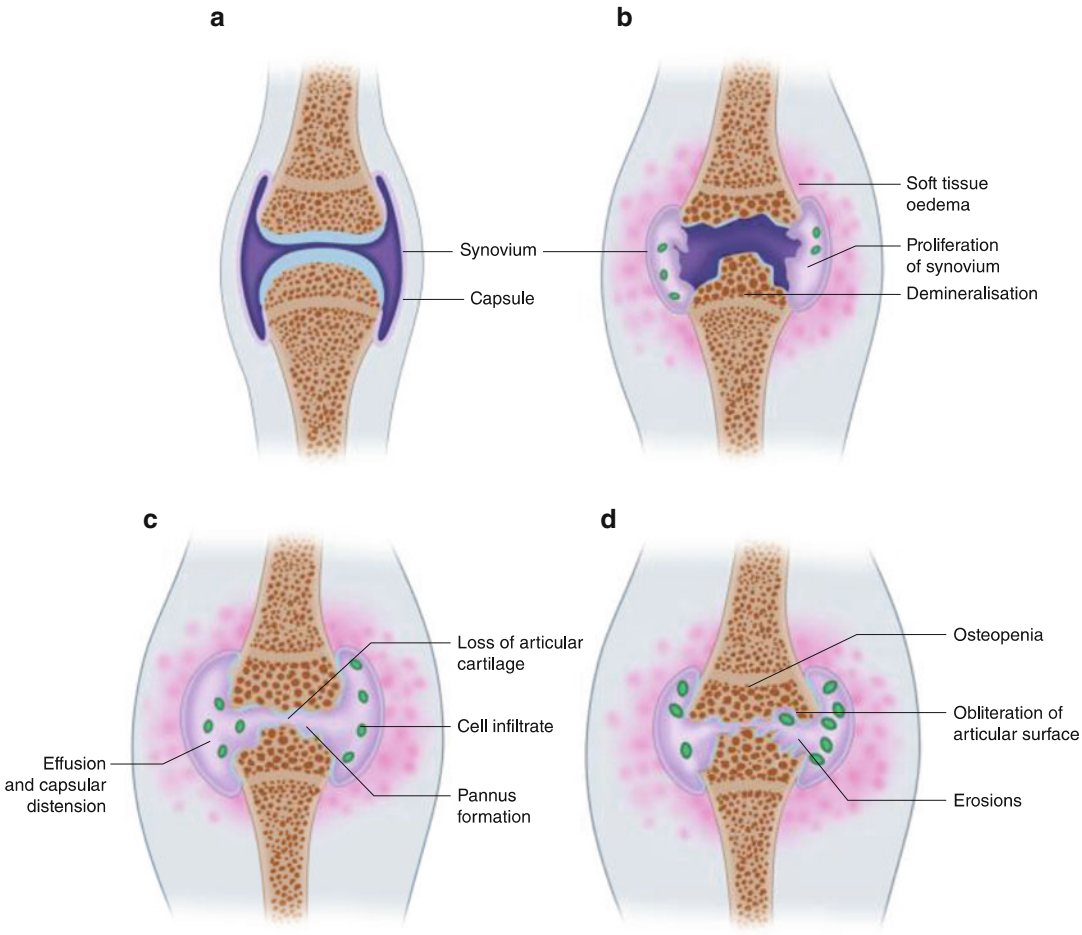

Fig. 1 Schematic diagrams showing the pathogenesis of rheumatoid arthritis. (**a**) Normal. (**b**) Synovial proliferation, periarticular soft tissue oedema, periarticular demineralisation and increase cellular activity in the synovium. (**c**) Synovial pannus extends across cartilage surface, capsular distension, joint effusion, soft tissue oedema, caudal erosion and osteopenia. (**d**) Loss of articular cortex, small osseous erosions, obliteration of articular surface, large marginal and central erosions and cysts formation. Cell infiltrate B cells, T cells and pro-inflammatory cytokine especially IL-6, IL-1 and TNF-alpha [14]

precursors together with Wnt inhibitors such as Dickkopf1 and sclerosis having significant roles in osteoclast dysregulation [50].

In addition, environmental factors are increasingly recognised in the pathogenesis of RA [33]. These include smoking and infection, both bacterial and viral such as Epstein-Barr [51, 52] and herpes viruses [53]. There is a close connection between RA and periodontal disease [54–56], and they share common clinical, immunological, serologic and epidemiological features [6].

Clinical Manifestations

Elderly-onset RA (EORA) is characterised by a lower female to male ratio, a more abrupt onset [30] involving the shoulders, higher disease activity and a more rapid functional decline [57]. There are several subsets of EORA which include polymyalgia rheumatica (PMR) and 'remitting' seronegative symmetrical synovitis with pitting oedema, among others [57]. Two incomplete

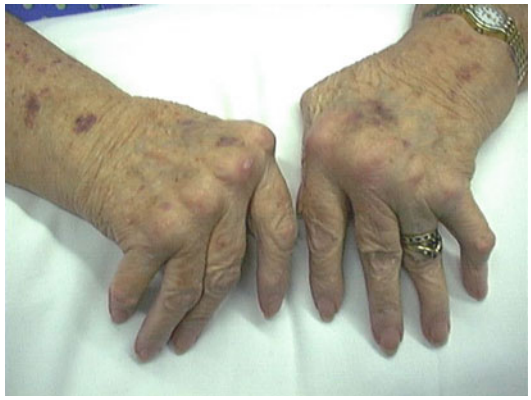

Fig. 2 Shows bilateral symmetrical deformities of hands and fingers typical of rheumatoid arthritis (Reproduced, with kind permission, from Prof. Nicholas Manolios)

subsets of EORA somewhat overlapping have been recognised, one exhibiting classical RA clinical picture and seropositivity and the other less severe and has a polymyalgia rheumatica-like appearance [26, 58], with shoulder involvement and absence of rheumatoid factor and usually follows a non-erosive course [26]. In one study, an initial clinical presentation resembling PMR was four times as frequent in EORA and less likely to have subcutaneous nodules or RF at disease onset [30]. In EORA, there are more radiographic damages.

The onset with YORA is usually insidious with early and progressive joint involvement. In about 25% of patients, it is acute or subacute [58]. There is symmetric joint involvement of the small hand joints or feet and the metacarpophalangeal and/or metatarsophalangeal joints, respectively [59]. Classically, in the hands, it is a bilateral symmetrical proximal process (Fig. 2). Malaise and fatigue occur late in the morning with stiffness for more than 30 min [59] or after prolonged activity. With progression, ulnar deviation of the fingers, flexion contractures, 'swan-neck' deformity (flexion of the distal interphalangeal with extension of the proximal interphalangeal joint) and boutonniere deformity (hyperextension of the distal interphalangeal joint with flexion of the proximal interphalangeal joints) are the common deformities seen. The differences between EORA and YORA are summarised in Table 1.

Table 1 Differences between elderly-onset RA (EORA) and young-onset RA (YORA)

	EORA	YORA
Age (years) peak onset	After 60	Third decade
Gender	M>F	F>M
Mode of onset	Acute with early systemic involvement	More insidious with early joint involvement
Pattern of joint involvement	Larger joints, upper limbs Shoulder joint	Smaller joints MCP and MTP joints
Rheumatoid nodules	Less frequent	More frequent
Rheumatoid factor	Less frequent	More frequent
	Higher titres	
Sedimentation rate/C-reactive protein	Higher rates	High
	At onset	
Joint score outcome	Lower score	Wider variation
Extra-articular manifestations	Less common	Common
Outcome	Better	Poor
Differential diagnosis	Polymyalgia rheumatica, crystal-related arthritis, remitting seronegative symmetrical synovitis with pitting oedema (RS3PE), hepatitis C virus-related arthritis, paraneoplastic disease	SLE, systemic sclerosis, polyarthritis, dermatomyositis

Information sources: Olivieri et al. [26], Deal et al. [30] and Bajoochi et al. [31]

RA is often associated with extra-articular features. Subcutaneous nodules typically occur on the ulnar border of the forearm, the olecranon and less frequently the cranium, sacrum and ischial tuberosity and are found in about 15–30% of all cases of RA when the disease is usually long-standing. They are firm in consistency and show little movement over the underlying tissue. They have adverse prognostic factors especially when they appear early in the disease. Patients with rheumatoid nodules are usually RF positive and usually develop erosive disease. Elderly patients at the onset are

less likely to have subcutaneous nodules [30]. Olecranon bursitis is not an uncommon finding in RA. They may feel soft or firm depending on the amount of fluid in the bursa and found on the extensor aspect of the elbow joint.

The signs associated with extra-articular involvement include vasculitis, Felty's syndrome, pulmonary fibrosis, cardiac involvement and haemorrhagic manifestations [58]. Vasculitis manifest as nail-bed or nail-fold haemorrhages in the fingers. More extensive vasculitis may involve the viscera causing infarction or gangrene and less commonly involve the cerebral, renal and coronary arteries. Other manifestations of vasculitis are leg ulcers and mononeuritis multiplex. Sjogren's syndrome characterised by keratoconjunctivitis sicca (dry eyes) and xerostomia (dry mouth), lymphadenopathy, Felty's syndrome (RA with splenomegaly and leucopenia) and pleural and pericardial manifestations occurs with other extra-articular manifestations. Interstitial lung disease, classical hand deformities and Sjogren's syndrome are less common at late onset [28].

Laboratory Findings

The erythrocyte sedimentation rate is elevated, and the rheumatoid factor (RF) is positive in about 70% of the cases. A recently added anti-CCP (anti-cyclic citrullinated peptide antibody) is highly specific (>98%) and has moderate sensitivity for diagnosis of RA [60]. RA patients may have RF negative but may have positive anti-CCP antibodies. Anti-CCP antibody (+RF) positivity is associated with an increased risk of erosive disease in RA. In a study of anti-CCP antibodies in the differential diagnosis of EORA and polymyalgia rheumatica (PMR), the investigators found that anti-CCP antibodies were negative in PMR. EORA patients presented positive anti-CCP antibodies at the beginning, and seronegative EORA patients were anti-CCP antibodies positive at the onset [61]. Patients with clinical symptoms of PMR and anti-CCP antibodies should be taken as highly suggestive of EORA [62]. EORA is characterised by the absence of RF. A very high titre signifies a worse prognosis. The availability of highly specific tests such as antibody to anti-citrullinated protein antibodies has improved diagnosis [63]. Despite the high sensitivity of ACPA, there is a demand for new serological markers to improve the diagnosis, and several autoantigens have been described [64].

A normocytic normochromic anaemia may be seen in about 70% of the cases and with blood loss, iron deficiency anaemia. The radiological changes are soft tissue swelling seen in the first few months of the disease and subsequently, periarticular osteoporosis and marginal erosions. In the large joints, there is marked periarticular osteoporosis with narrowing of the joint space Erosions may or may not be present.

Diagnosis

The diagnosis of RA is essentially a clinical one based on history and physical examination [65]. Laboratory tests and imaging studies may help to confirm and establish the diagnosis. The clinical features are the mode of onset, pattern of joint involvement with pain and stiffness and nodules and erosions on X-ray. Essential features in establishing a diagnosis include examination of the joints, assessments of extra-articular manifestations, laboratory tests and radiological examinations. The American College of Rheumatology [66] had developed criteria to help and guide clinical diagnosis.

The differential diagnosis of YORA may include any of the causes of arthritis. When serological tests are negative at the onset, it may be difficult to distinguish from other causes of polyarthritis such as SLE. Early progressive systemic sclerosis, dermatomyositis, polymyositis and polyarthritis may have features that resemble RA. SLE has skin lesions on light-exposed areas (photosensitivity), frontal hair loss, Raynaud's phenomenon, renal involvement and non-erosive arthritis with positive antibodies to double-stranded DNA and anti-nuclear antibodies.

The differential diagnosis of EORA is somewhat different and includes true polymyalgia rheumatica, crystal-related arthritis (pseudogout and polyarticular gout), elderly-onset spondyloarthritis,

remitting seronegative symmetrical synovitis with pitting oedema syndrome, paraneoplastic disease and hepatitis C virus-related arthritis [67]. To arrive at a diagnosis, knowledge of the specific features of these diseases is required. HCV arthropathy should be considered in the differential diagnosis even in the absence of liver disease. In one study of 25 patients who were HCV-RNA positive (genotype 1b in 65%), 68% had symmetric polyarthritis, 68% had morning stiffness, 61% had RF positivity, 54% had elevated ESR and none had subcutaneous nodules or erosive disease [68]. The RS3PE syndrome is a manifestation of seronegative RA in the elderly with a good prognosis. It occurs with a male to female ratio of 2:1. It usually presents as an acute symmetrical polyarthritis with oedema of the dorsum of hands and feet. Anti-CCP antibodies are very useful in identifying EORA patients with polymyalgic onset [18].

Management

Management includes both non-pharmacological and pharmacological practices. In elderly patients, treatment objectives should be kept simple and individualised for each patient, based upon potential side effects, coexisting comorbidities, use of concomitant medications [19], self-care capability, existing quality of life and practicability of follow-up. The mainstay of treatment is pharmacological.

Non-pharmacological strategies include (i) patient and caregiver education and (ii) physical activity. They should be practically orientated and conducted on a regular basis. It has been shown that aerobic and muscle strengthening exercises result in better outcomes in patients with RA [69]. Occupational therapy, bathing in hot mineralised water, tai chi, acupuncture and low-level therapy are among non-pharmacological interventions available, and patients often ask the general practitioner as to their usefulness [70].

Pharmacological

Early diagnosis and aggressive treatment [71] are beneficial in treating synovial inflammation of RA [38]. T cells, B cells and the interaction of pro-inflammatory cytokines (e.g. IL-6, TNF-alpha, IL-1) are involved in the pathogenesis of RA [14], and IL-6 has been linked to activation of the synovium and osteoclasts [72]. The development of biological agents that specifically block the cytokines has provided means for preventing disease progression and improving outcomes [73]. The drugs that inhibit TNF-alpha are etanercept, adalimumab, certolizumab, golimumab and infliximab, the drug that inhibits IL-6 is tocilizumab, the drug that blocks activation of T cells is abatacept, and the drug that causes depletion of B lymphocyte is rituximab [73]. These drugs especially in combination with methotrexate are most effective [73]. Better clinical and radiographic outcomes have been achieved with the early use of anti-TNF therapy in combination with methotrexate which can be maintained for up to 5 years after withdrawal of the former [63]. Although the new medications have shown considerable assurance and improve disease outcomes, they come with pronounced side effects [11] and increased costs. Recently, small molecules have been receiving attention with some of the protein kinase inhibitors [74]. When extracellular molecule, for example, IL-6 docks into cells, the kinase an intracellular enzyme is activated thus triggering an inflammatory response. A new drug baricitinib that inhibits Janus kinase 1 and 2 has been found to be promising, and in a trial in patients with inadequate response to biologic DMARDS, a daily dose of 4 mg orally was associated with clinical improvement at 12 weeks [75]. The search goes on for more effective evidence-based pharmacological treatments with less side effects, oral method of administration and reduced costs.

The aim of treatment is to minimise or prevent joint damage, preserve function and induce clinical remission [63, 76]. The therapeutic goals are the same in both groups (YORA, EORA), but specific treatments have to be adjusted in the context of patient's age and co-morbidities. The finding of early joint damage in patients with RA has underscored the importance of early recognition and treatment. Traditionally, treatment was based on a 'therapeutic pyramid' in which treatment increased as the symptoms worsened [77],

but this has been challenged and no longer valid [78]. Early aggressive treatment with a combination of drugs may be justified for the effectual treatment of RA [79].

Treatment in RA typically involves (i) non-steroidal anti-inflammatory (NSAIDS and simple analgesics), (ii) low-dose corticosteroids and often used in combination and (iii) disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, sulphasalazine, gold, hydroxychloroquine, leflunomide or cyclosporine. Over the past few years, drug development for rheumatoid arthritis has emerged with the introduction of biological agents (etanercept, adalimumab, infliximab) designed with strict reference to RA pathophysiology [41, 80].

It is important that for every single patient, the risk/benefit ratio relating to their use must be closely and correctly assessed. The management of RA in the elderly requires special attention to the co-morbidities and increased propensity to adverse reactions. Treatment in the elderly requires caution because of the increased age-related risks relevant especially to the renal, cardiovascular and gastrointestinal systems. Care is needed in the use of non-steroidal anti-inflammatory and prednisone in the elderly [21]. In the elderly, the increased susceptibility is related to the impairment of renal function and to the different metabolism of aged individuals. The treatment has to be considered in relation to long-term outcome and manner of onset of the disease. There are several indicators of poor outcome in RA, for instance, the number of joints involved, age of onset, the presence of RF factor, elevated ESR, presence of extra-articular features such as nodules and early radiological changes (Box 1).

Box 1 Indicators of Poor Outcome

I. Major Indicators

Large number of swollen joints; positive rheumatoid factor

Positive anti-CCP; presence of nodules

Elevated sedimentation rate; elevated C-reactive protein

Box 1 Indicators of Poor Outcome (continued)

II. Other indicators at onset of disease

Onset in early adulthood; onset in elderly males

Insidious onset; high disease activity at onset

Early involvement of large joints; extra-articular features (nodules, etc.)

Early radiological changes

Information source: Rindfleisch and Muller [59]

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are symptom modifying and not disease modifying [81]. All NSAIDs inhibit prostaglandin synthesis by blocking cyclooxygenase (COX) activity. The older and newer NSAIDs differ in their effect on two cyclooxygenase isoenzymes. Cox-1 inhibition is associated with greater potential to gastrotoxicity, while selective Cox-2 inhibition is associated with decreased gastrotoxicity. Both selective Cox-2 inhibitors and non-selective Cox-1 have similar effects in raising the blood pressure and reducing renal function. With increasing age, the safety profile of NSAIDs worsens, and an age-related risk evaluation pertaining specifically to renal, cardiovascular and gastrointestinal systems needs to be done [82]. NSAIDS should be used with caution in elderly patients for they are likely to experience adverse gastrointestinal and renal effects [83]. Alternate therapies have to be considered if there are risk factors.

Glucocorticoids

Prednisone and prednisolone are used for the management of inflammatory joint disease in the elderly especially in polymyalgia rheumatica and in remitting seronegative symmetrical synovitis with pitting oedema [81]. If glucocorticoids are prescribed, it should be the lowest dose and for the shortest period possible [66]. The elderly are at particular risk of glucocorticoid-induced osteoporosis. They should be given advice on lifestyle

factors known to affect bone such as weight bearing activity, adequate dietary calcium intake, to stop smoking and limit alcohol consumption. Calcium 1,500 mg and vitamin D 400–800 IU daily supplements are recommended [66], and if and when high doses of glucocorticoids are required, prophylactic bisphosphonates should be considered. Patients should be monitored for osteoporosis risk, blood pressure monitored and blood glucose estimated. Injection of glucocorticoids is safe and effective intervention when a single inflamed joint causes severe disability [66].

Disease-Modifying Anti-rheumatic Drugs (DMARDs)

The efficacy and tolerability of the DMARDs are similar in both age groups. DMARDs and the newer biological DMARDs are the only drug treatments that can minimise or prevent joint damage, preserve function and induce clinical remission [76]. Current strategies lay stress on the early diagnosis and therapeutic intervention based on the use of DMARDs with objective monitoring of activity [63]. DMARDS should be considered for all patients with RA, and patients should be treated early as possible to control symptoms and delay progression [84, 85]. When started early, DMARDs improve clinical remissions in patients at risk of persistent and or erosive arthritis. More than a dozen drugs or drug classes of DMARDs are currently in use in RA. The combination of several DMARDs has shown increased efficacy over monotherapy without significant increase in toxicity [86] (Table 2):

(i) Methotrexate (MTX) is the first choice in moderate and severe disease in patients at risk of persistent or erosive arthritis. Twenty percent of the medication prescribed by primary care physicians for RA is methotrexate [87]. Its efficacy is superior to most other DMARDs but has a better advantage-disadvantage profile and can be used in combination with other conventional DMARDs. Particularly in the first year of treatment, it is associated with risks of cytopenia, pneumonitis and hepatotoxicity [88]. It is usually given as a single weekly dose starting at 5–10 mg PO once a week and to be increased in 4–6 weeks by 2.5 mg −10 mg up to a maximum of 15–25 mg [89]. It is safe and effective in EORA but should be used with caution. Folic acid 5 mg is taken orally once or twice a week preferably not on the day of methotrexate [89]. Combination of methotrexate and anti-TNF-alpha therapy is said to achieve better clinical and radiographic outcomes and can be carried on for up to 5 years after withdrawal on anti-TNF-alpha therapy [63]. Monitoring includes monthly FBC and LFTs for the first 6 months and then 2–3 months subsequently. If used in combination with sulphasalazine, hydroxychloroquine or leflunomide at least monthly [66, 89, 90]. The adverse effects include mouth ulcers, rash, alopecia, nausea, diarrhoea, nodulosis and abnormal LFTs.

(ii) Leflunomide may be used alone or in combination. It is less well tolerated but is as effective in slowing progression of joint damage [91]. It is given 10–20 mg once daily. Monitoring FBC and LFTs at baseline monthly for the first 6 months. Adverse effects are nausea, diarrhoea, alopecia and rarely hepatitis, and it is highly teratogenic.

(iii) Sulfasalazine is effective alone in seronegative RA and in combination with methotrexate and hydroxychloroquine in ssevere disease [48]. Beginning with 500 mg orally daily, the dose is increased by 500 mg a week to a maximum of 3 gm daily in divided doses [89]. Monitoring FBC and LFT at baseline monthly for the first 3 months and then every 3 months [66, 89, 90]. The side effects are diarrhoea, nausea, mouth ulcers, rash, alopecia, abnormal LFTs and rarely leucopenia.

(iv) Hydroxychloroquine used alone or in combination is safe and effective [92]. Hydroxychloroquine retinopathy is a rare complication, and an ophthalmic review is required at baseline and then every 6–12 months and full blood count after 1 week of treatment. The side effects are nausea, headaches, retinal toxicity and myopathy.

Table 2 Systemic agents used in the treatment of rheumatoid arthritis

Systemic agent	Pretreatment assessment	Monitoring and precautions	Contraindications
DMARDs			
i. Methotrexate	History and examination FBC, LFT, U&E serum creatinine monthly for the first 6 months, then 1–2 months	FBC, LFT,U&E serum creatinine	Severe renal, hepatic disease, myelosuppression, excessive alcohol consumption, acute infection, immunodeficiency, interactive drugs, diabetes or extreme obesity
		Avoid drugs which are interactive	
ii. Leflunomide	Same as for methotrexate		
iii. Azathioprine	History and FBC, LFT, U&E urinalysis	FBC, LFT weekly treatment and then every 1–3 months, urinalysis, avoid drugs which interact	Methotrexate, porphyria, infection significant hepatic damage
Sulphasalazin	FBC, LFT for the first 3 months	Hypersensitivity to salicylates then every 3 months	Or sulphonamide derivatives
	FBC and LFT		
v. Hydroxychloroquine	History and examination	FBC after 1 week of treatment	Hypersensitivity to quinolones, retinopathy
	Ophthalmological review	Ophthalmological review every 6–12	
vi. Sodium aurothiomalate injectable gold	History and examination	FBC, LFT every 1–2 weeks for the first 5 months and then monthly	Toxicity to gold, renal, hepatic, impairment, myelosuppression
	FBC, LFT urinalysis		SLE, severe or chronic skin conditions
Biological DMARDs			
TNF-alpha			
Inhibitors-infliximab Adalimumab	Hepatitis B and C Tuberculosis	FBC, LFT monthly 3–6 months, monitor reactivated tuberculosis	Tuberculosis, hepatitis B and C, septic arthritis MS, malignancy, CHF
Etanercept			
Golimumab			
IL-6 receptor antagonist-tocilizumab		Signs of heart failure	
Cell-targeted		Pulmonary sepsis	
Abatacept			
Rituximab			

Sources of information: National Prescribing Service Limited (NPS) [89], Amer Coll Rheumat [66] and Olsen and Stein [90]

Biological DMARDs (bDMARDs)

Biological therapies have the potential to revitalise the treatment of RA and are designed to neutralise inflammatory cytokines either by blocking the pro-inflammatory cytokines or decreasing the cytokine production through the B and T lymphocytes. Several biological treatments are now available. The bDMARDs that act as cytokine blockers can inhibit (i) tissue necrosis factor (golimumab, etanercept, infliximab, adalimumab) and (ii) interleukin-6 (tocilizumab). bDMARDs that target the cells, include (i) CD20 on B cells (rituximab) and (ii) those that cause interaction between T cells and antigen-presenting cells (abatacept) [63]. In a systematic review of 20 randomised controlled trials, adalimumab, etanercept and infliximab were found to be effective treatments compared with placebo in RA patients who were not well controlled on conventional DMARDs, improving control of symptoms and function and slowing radiological changes in

joints [80]. An increased risk of serious side effects cannot be ruled out when methotrexate is used in combination with adalimumab and infliximab [80]. TNF-alpha antagonists have increased the therapeutic opportunities for aged RA patients. TNF inhibitors have an increased risk of infection by bacterial, atypical fungal and opportunistic pathogens [88], and screening for tuberculosis should be done in all TNF inhibitors [88]. Janus kinase inhibitors interfere with the signalling through type 1 and II cytokine receptors and have been shown to be critical in rheumatoid arthritis [93]. Tofacitinib an oral Janus kinase inhibitor is effective in the treatment of rheumatoid arthritis, and adverse effects are mild, which include hyperlipidaemia and cytopenias [94].

Impact

Arthritis is the major cause of disability among older people. Women have a greater disability and prevalence rates [95]. Rheumatoid arthritis and other rheumatic conditions are large and growing health problems. The best estimates of the US prevalence and number of individuals afflicted with RA were 1.3 million in 2015 [96]. Rheumatoid arthritis is a severe disabling illness with deleterious effects [97] resulting in impairment of function and systemic complications [98]. It affects every aspect of daily life. RA impacts health, threatens the independence and has large economic and health costs [99]. It causses disability that results being house bound and is a risk for institutionalisation [95]. It interferes with basic activities such as self-care and walking. Persistent pain, fatigue and psychological stress are problems from the patient's perspective [97, 100]. Costs increases with the duration of the disease, and women are more affected than men in health status, social impact and out-of-pocket costs [99]. Physical distress can lead to negative emotional states such as depression, anxiety and difficulties with social interaction. Health-care system bears the increase of load in patients with high levels of disability resulting from interventions such as surgery and social care costs [100]. Health-related quality of life (QOL) in

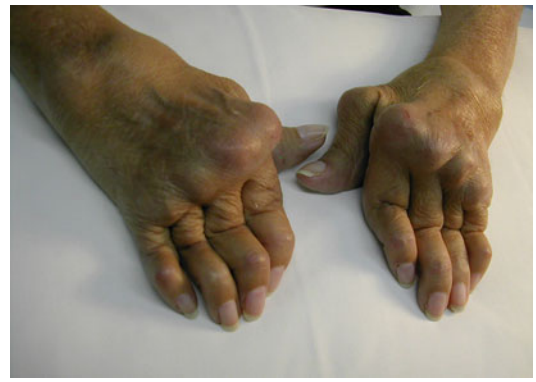

Fig. 3 Rheumatoid arthritis showing severe destructive processes and deformities of the fingers with severe impairment of function (Reproduced, with kind permission, from Prof. Nicholas Manolios)

patients with RA is significantly impaired as a result of impaired physical function due to deformities and severe destructive processes (Fig. 3), pain and fatigue associated with the disease [101]. Patients with early RA were seen to progress to significant disability within a few years [100] (Fig. 4). Clinicians must be aware that inadequate management of RA will lead to increasing functional disability and reduced quality of life [102]. There is evidence that the elderly-onset RA (EORA) is less severe than the young-onset RA (YORA). There are several subsets of EORA, and in about 50% of the patients, it is an aggressive disease and has worse prognosis in terms of functional capacity [26]. Rheumatoid arthritis is the most common autoimmune disease in Australia and affects about 16.7% of the population with almost 2% disabled or handicapped with arthritis [103]. It causes severe disability, and 20–30% become permanently work disabled within 2–3 years of diagnosis [59] (Box 2).

Box 2 Key Points: Rheumatoid Arthritis

- One-third of patients acquire RA after the age of 60 years [19].
- In the elderly, RA takes two forms (i) continuing into old age with younger-onset RA (YORA) and (ii) elderly-onset RA (EORA).

(*continued*)

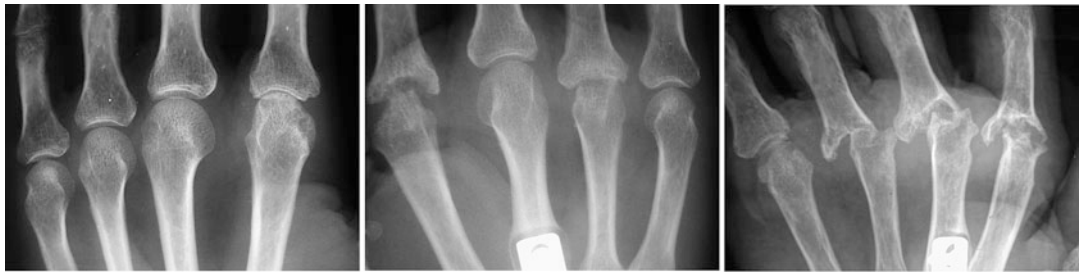

Fig. 4 Shows rapid progression. (**a**) 1996; (**b**) 1997 and (**c**) 2002. (**c**) Show bone erosion, bone displacement, deviation of the fingers and destruction of the joint (Reproduced, with kind permission, from Prof. Nicholas Manolios)

Box 2 Key Points: Rheumatoid Arthritis
(continued)

- Elderly-onset RA (EORA) is characterised by a lower female to male ratio, a more abrupt onset [30] involving the shoulders, higher disease activity and a more rapid functional decline [57].
- Two incomplete subsets of EORA somewhat overlapping have been recognised: one exhibiting classical RA clinical picture and seropositivity and the other less severe and has a polymyalgia rheumatica-like appearance [26, 58].
- Anti-CCP (anti-cyclic citrullinated peptide antibody) is highly specific (>98%) and has moderate sensitivity for diagnosis of RA [60].
- Patients with clinical symptoms of PMR and anti-CCP antibodies should be taken as highly suggestive of EORA [62].
- The differential diagnosis of EORA is somewhat different and includes true polymyalgia rheumatica, crystal-related arthritis (pseudogout and polyarticular gout), elderly-onset spondyloarthritis, remitting seronegative symmetrical synovitis with pitting oedema syndrome, paraneoplastic disease and hepatitis C virus-related arthritis [67].
- The therapeutic goals are the same in both groups (YORA, EORA), but specific treatments have to be adjusted in the context of patient's age and co-morbidities.

Box 2 Key Points: Rheumatoid Arthritis
(continued)

- NASAIDs are symptom modifying and not disease modifying [81]. They should be used with caution because of the recent finding of potential side effects. Alternate therapies have to be considered if there are risk factors.
- Methotrexate is the first choice in moderate and severe disease in patients at risk of persistent or erosive arthritis.
- Adalimumab, etanercept and infliximab are effective treatments for patients who were not well controlled on conventional DMARDs [80].
- The role of the primary care physician is (i) early referral for treatment, (ii) ongoing monitoring and titration of medication and (iii) patient education and review.
- Tofacitinib an oral Janus kinase inhibitor is effective in the treatment of RA [94].

Multiple Choice Questions

1. The following are true in the management of RA in the elderly, except:
   A. Early diagnosis is crucial.
   B. Methotrexate is safe and effective in the elderly but should be used with caution.
   C. Elderly patients on NSAIDs with a history of peptic ulcer do not need gastric protection.
   D. Special attention to co-morbidities (age-related risks especially renal, cardiovascular

and GI systems) and increased propensity to adverse reactions.

2. The following treatment of rheumatoid arthritis (RA) is true, except:
   A. Folic acid 5 mg once or twice a week preferably not on the day of the methotrexate.
   B. Side effects such as steroid-induced osteoporosis are rare in elderly RA patients.
   C. Hydroxychloroquine alone or in combination is safe and effective but an ophthalmic review at baseline and thereafter every 6–12 months.
   D. Biological DMARDs improve control of symptoms, function and slow radiological changes in the joints.

MCQ Answers

1 = C; 2 = B

Short Answer Questions

1. List four clinical features that will distinguish elderly-onset rheumatoid arthritis (EORA) from young-onset rheumatoid arthritis (YORA).
2. List four factors that indicate poor outcome in rheumatoid arthritis.

SAQ Answers

1. (i) Elderly-onset RA usually involves proximal joints (shoulders, hips); (ii) Rheumatoid factor is less frequently positive in EORA; (iii) Rheumatoid nodules are less frequently present; (iv) Acute onset with early systemic involvement
2. (i) Positive rheumatoid factor; (ii) Positive anti-CCP antibody; (iii) Presence of nodules; (iv) Large number of swollen joints

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Polymyalgia Rheumatica

56

Contents

Abstract

Polymyalgia rheumatica usually affects persons over the age of 60 years and the average age is 72 years and women are more affected than men. It is characterized by proximal myalgia of the shoulder and pelvic girdles accompanied by morning stiffness and nonspecific systemic symptoms. Bilateral subacromial subdeltoid bursitis is deemed to be a feature of PMR. About 16–21% of the patients with PMR develop giant cell arteritis (GCA) and about half the patients with GCA have associated PMR. PMR shows prompt and good response to corticosteroids.

Keywords

Polymyalgia rheumatic · Giant cell arteritis · PMR-like syndrome · Bilateral subacromial subdeltoid bursitis

Introduction

Polymylagia rheumatica (PMR) is characterized by proximal myalgia of the shoulder and pelvic girdles accompanied by morning stiffness and nonspecific systemic symptoms. It is a relatively common clinical syndrome, and its frequency varies by country with highest rates in Northern Europe [1]. Women are affected two to three times more often than men [2]. In patients over the age of 50 years the annual incidence is 20–50/100,000 [3]. Lawrence et al. [4] estimated the prevalence and number of individuals with PMR in the United States in 2005 to be 711,000 and giant cell arteritis 228,000.

Clinical Manifestations

It usually affects persons over the age of 60 years and the average age is 72 years [5], and women are more affected than men [2]. It is characterized by

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_59

severe pain and stiffness of at least two or three areas, shoulders, neck, or hip [6]. It may unilateral but usually becomes bilateral in few weeks. The morning stiffness usually last for more than an hour and stiffness after activity (gelling phenomenon). It is the most frequent symptom and is exacerbated by movement and involves the shoulder and pelvic girdles and the neck [1, 6]. Often there is low grade fever, loss of weight accompanied by fatigue, malaise [7], and depression. Swelling of the extremities is uncommon. There is no muscle weakness or evidence of muscle disease on electromyography.

About 16–21% of the patients with PMR develop giant cell arteritis (GCA), and about half the patients with GCA have associated PMR [8]. The focus for GCA appears to localize in elastin-containing arteries and can also cause myalgias [9]. Patients diagnosed as CGA and or PMR are found to have small vessel vasculitis and is considered a diagnostic criterion for PMR [10]. Distal extremities swelling with pitting edema over the dorsum of the hands have been described with PMR [11] in about 12% of patients [12], and it has been suggested that PMR and remitting seronegative symmetrical synovitis with pitting edema (RSPE) syndrome are part of the same clinical syndrome [13]. Furthermore, it has been shown that PMR-like syndrome occurs with elderly onset spondyloarthritis [14]. Distinguishing features between EORA, YORA, and PMR are shown in Table 1.

Diagnosis

The diagnosis of PMR is based on clinical manifestations [17] and elevated levels of inflammatory markers [2, 18]. More recently, the European League Against Rheumatism and the American College of Rheumatology (EULAR/ACR) [19, 20] developed criteria and it has been shown that new onset PMR patients are able to distinguish PMR from RA and other inflammatory articular disease better [21] (Table 1). The sedimentation rate is frequently elevated and usually is greater than 50 mm/h, but in some

Table 1 Distinguishing features between EORA, YORA, and PMR

	Elderly onset RA	Younger onset RA	Polymyalgia rheumatica
Age of onset	60 years or over	30–50 years	After 60 years
Male: Female	1:2	1:1	1:2
Mode of onset	Acute	Insidious	Acute, subacute
Symptoms at onset	Acute systemic activity		Severe pain, stiffness
Pattern of joint involvement	Shoulder/hip	MCP/PIP joints	Shoulder/hip/neck
Clinical course	Less erosive course	More erosive course	Self-limiting (1–3 years)
RA factor	Less frequently	More frequently	Negative
ESR	Increased	Increased	40 m/Hg or over
Associated symptoms		Extra-articular manifestations	Giant cell arteritis systemic complaints
Differential diagnosis	Pseudogout with crystalline synovitis, true PMR, elderly-onset spondyloarthritis, hepatitis C related arthritis, remitting seronegative symmetrical arthritis with pitting edema	Osteoarthritis, pseudogout with crystalline synovitis, EORA, SLE, systemic sclerosis	RA, OA, fibromyalgia hypothyroidism, GCA, depression, polymyositis

Information sources: Mihet and Matteson [5]; Olivieri et al. [13]; Deal et al. [15]; Bajoochi et al. [16].

patients it is only mildly elevated or normal [1]. The C-reactive protein levels are usually elevated and is more sensitive than ESR [5]. A normocytic normochromic anemia may be present. The liver function tests are normal, but the alkaline phosphatase may be mildly increased. In a minority of patients (about 10%) with polymyalgic symptoms due to similarities in the presentation the correct diagnosis of LORA, PMR, and GCA can be delayed [18]. A persistent raised plasma viscosity, a positive rheumatoid factor, and the presence of HLA-DRB1*04 may suggest RA and GCA [18] and in older people RA and spondyoarthritis can mimc PMR [20]. In the EULAR/ACR criteria, ultrasound has been included in the scoring algorithm [19]. Bilateral subacromial subdeltoid bursitis is deemed to be a feature of PMR [22].

Treatment

PMR shows prompt and good response to corticosteroids [1, 12] and is initiated at 10–15 mg/day prednisone for 2–4 weeks. When patient becomes asymptomatic, the dose can be lowered by 1–2.5 mg/q 2–4 weeks to find the minimum dose needed to remain symptom free regardless of the ESR. Once 10 mg is reached taper by 1 mg/day decrements q 4 weeks. Some may be able to discontinue in a year but mostly within 2 years. Relapses are common and varied from 46% [23] to 68.3% [24] especially where prednisolone is tapered off prematurely. There are some who do not respond to the initial doses of steroids and require high doses. CGA is treated with oral prednisolone 40–60 mg/daily [1]. Other factors that require large doses of corticosteroid are coexisting polymyalgia and giant cell arteritis [25] and those with highly elevated inflammatory markers [26]. Combination therapy with prednisolone and methotrexate with newly diagnosed PMR reduced the incidence of flare-ups and the amount of prednisolone required to maintain remission [27]. There was however no reduction of steroid-related side effects [26].

Impact

In some instances, patients with PMR may require high doses of corticosteroid and prolonged therapy, especially in those with high ESR and serum levels of interleukin-6. The elderly pose serious problems with the use of corticosteroid therapy due to adverse effects. These include cardiovascular diseases, fracture risk, infections, and diabetes, among others. There was a fourfold risk of fracture in both men and women with corticosteroid therapy [28]. There was a significant risk of developing cataract in a long-term follow-up of patients with PMR on corticosteroids [13] (Box 1).

Box 1 Key Points: Polymyalgia Rheumatica

Averag age of onset is just over 70 years and is more common in the females [15].

Involves at least two or three areas – shoulders, neck, or hip [15].

Symptomatology include – morning stiffness, stiffness after activity (gelling), low grade fever, loss of weight, and anemia [7].

C-RP is elevated more often than ESR [5].

About 16–21% of the patients with PMR develop giant cell arteritis (GCA), and every patients with PMA should be considered a risk for GCA [2].

Distal extremity swelling with pitting edema over the dorsum of the hands have been described with PMR [11].

PMR shows a prompt and good response to corticosteroids [1, 12].

Relapses are common and varied between 46% and 68% [20, 21].

Multiple Choice Questions

1. Which of the following in polymyalgia rheumatica (PMR) is INCORRECT?
   A. Is twice more common in the females.
   B. C-reactive protein is usually elevated.

C. A microcytic hypochromic anemia may be present.
D. 15% of the patients develop giant cell arteritis (GCA).

MCQ Answers

1 = C

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Psoriatic Arthropathy

57

Contents

Abstract

Psoriatic arthritis (PsA) presents as a diverse group of arthritis ranging from peripheral monoarticular and polyarticular disease to axial skeletal involvement. PsA in the elderly shows some differences from the young-onset disease. They have a higher involvement of active joints, foot erosions and elevation of CRP and synovial IL-1 beta and IL-beta, and the progression rate is higher than in the younger group. About 40% of patients with PsA show the presence of spondylitis. PsA also confers a significant increase in mortality risk, and the major causes of death among patients with psoriasis include myocardial infarction, respiratory causes and cancer. PsA patients have reduced quality of life and functional capacity compared to psoriasis patients.

Keywords

Psoriatic arthritis · Psoriasis · Quality of life · Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE)

Introduction

Psoriatic arthropathy (PsA) is a chronic inflammatory disease that develops in patients with psoriasis and involves the peripheral joints and spine and is usually seronegative for RF [1]. It affects about 1% of the population. It develops in 7–42% of patients with psoriasis [2], and 95% of them are RF negative. About 30% of patients with psoriasis will develop PsA according to a study from Sweden [3]. It presents as a diverse group of arthritis ranging from peripheral monoarticular and polyarticular disease to axial skeletal involvement [4]. Elderly onset PsA (EOPsA) has a more severe onset and more destructive outcome than in younger subjects [5]. PsA in the elderly shows some differences from the young-onset disease [4, 5]. They have a higher involvement of active joints, foot erosions and elevation of CRP and synovial IL-1 beta and IL-beta, and the progression rate is higher than in the younger group [5]. PsA now belongs to the spondylitic arthropathy group together with ankylosing spondylitis, reactive arthritis, inflammatory bowel

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_56

arthritis and related arthritis. Those that do not meet the criteria are designated undifferentiated SpA [6, 7]. About 40% of patients with PsA show the presence of spondylitis [8]. Genetic factors are considered to be important, and the strongest association is with HLA-C*06 gene itself [9], and HLA-C* 06 allele has been shown to be increased in PsA patients who also showed an earlier onset of their psoriasis [10]. In PsA patients with HLA-27 positivity, the joint involvement appears earlier, and the interval between the onset of psoriasis and arthritis is longer than in those without the marker [11].

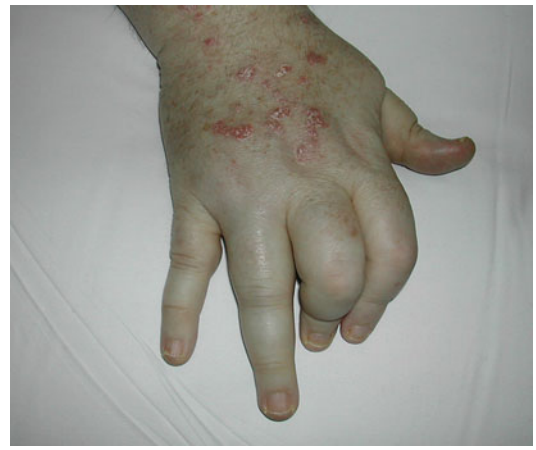

Fig. 1 Psoriatic arthritis with skin lesions shows 'sausage fingers' in which the fingers become uniformly swollen involving all three joints (Reproduced, with kind permission, from Prof. Nicholas Manolios)

Clinical Manifestations

There are five patterns of clinical presentations of psoriatic arthropathy [12]:

(i) Common single joint involvement or few random joints (70%)
(ii) Classic pattern – distal interphalangeal (DIP) joints
(iii) Spondylitis with or without peripheral joint involvement
(iv) Indistinguishable from rheumatoid arthritis (15%)
(v) Aggressive with 'arthritis mutilans'

The clinical spectrum of PsA ranges from typical features of spondyloarthropathy to pseudo-rheumatoid disease [1]. They are not absolutely discrete and symptoms overlap. Symptoms include pain in the joints, stiffness, swelling, dactylitis and nail changes [13, 14] (Fig. 1). Psoriatic nail changes are strongly associated with the development of psoriatic arthritis with DIP joint involvement. Resorption of the terminal phalanx may lead to telescoping of all the fingers and toes (Fig. 2) More recently, remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) [15] has been the first manifestation of psoriatic arthropathy. The syndrome RS3PE has been associated with other rheumatic diseases such as PMR, elderly onset RA (EORA),

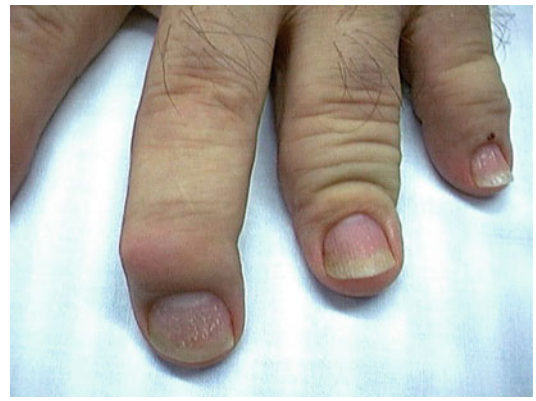

Fig. 2 Shows shortening (telescoping) of the terminal phalanx of all the fingers (Reproduced, with kind permission, from Prof. Nicholas Manolios)

ankylosing spondylitis and spondyloarthropathies [1, 16]. Apart from arthritis, other manifestations of psoriasis in the elderly are inverse psoriasis, drug-induced or drug-aggravated psoriasis and life-threatening forms such as erythrodermic or acute pustular psoriasis when urgent referral to a dermatologist is vital [17]. In a study of the clinical features of late-onset psoriatic arthritis (>65 years) compared to early-onset (<65 years), the investigators found that the male/female ratio was 9/3,

HLA-B27 was negative, and about a third of them had polyarticular involvement [4].

Treatment

The first line of treatment is with the NSAIDS to reduce and control the inflammation [18]. Corticosteroids are used for intra-articular injections to reduce the swelling and stiffness [19]. If with the use of NSAIDs there is no acceptable control, the second-line drugs, the DMARDs, such as methotrexate, sulphasalazine, cyclosporine and leflunomide [17] are added to the treatment regimen. An advantage of immunosuppressant drugs is that it also treats the skin condition. The recent advent of a new class of drugs (biologic DMARDs) using the recombinant DNA technology has increased focus in the diagnosis and treatment of psoriatic arthritis as more new and more effective drugs than the traditional disease-modifying agents have become available [20]. Drugs such as the TNF-alpha inhibitor are now available, for example, infliximab, etanercept and adalimumab, and have significant efficacy in PsA to date [14]. They are being increasingly used but are usually reserved for the severe cases. At present, the long-term safety of these biological agents is not known. There are factors which portend a poor prognosis (Box 1). Methotrexate, retinoic acid derivatives and psoralen plus ultra-violet light are used in patients with severe skin involvement [21]. In the elderly, topical applications include corticosteroids, tar and dithranol preparations, calcipotriol and tazarotene [16].

Box 1 Factors that May Portend Poor Prognosis

Strong family history of psoriasis
- Early onset
- Females
- Expression of HLA-B27, HLA-DR3 or HLA-DR4 alleles
- A polyarticular or erosive arthritis

Impact

Psoriatic arthritis (PsA) is associated with a wide range of problems which include symptoms relating to the skin and musculoskeletal disease to difficulties with day-to-day activities, social interactions and work from the patient's perspective [22]. Patients with PsA have an increased risk of developing cardiovascular disease and metabolic syndrome [23]. PsA also confers a significant increase in mortality risk, and the major causes of death among patients with psoriasis include myocardial infarction, respiratory causes and cancer [23]. Psychological distress often leads to anxiety, depression and reduced social interaction. Some of the patients with PsA have mild disease, and about 29% develop severe, rapid destruction of the joints [24], and if followed for more than 10 years, more than half have five or more deformed joints [24]. PsA patients have reduced quality of life and functional capacity compared to psoriasis patients [25]. Patients with psoriasis and psoriatic arthritis experience psychological stress which can lead to fatigue, poor sleep, depression, anxiety, pruritis, social disconnection and isolation [26]. Furthermore, because of physical limitations, direct costs such as disability and lost productivity result in total costs of care [13] (Box 2).

Box 2 Key Points: Psoriatic Arthritis

Psoriatic arthropathy may arise, with or after, and often as long as two decades after the onset of the skin disease.

It presents as a diverse group of arthritis ranging from peripheral monoarticular and polyarticular disease to axial skeletal involvement [4].

Elderly onset PsA (EOPsA) has a more severe onset and more destructive outcome than in younger subjects [5].

The clinical spectrum of PsA can range from typical features of spondyloarthropathy to pseudo-rheumatoid disease [1].

(*continued*)

Box 2 Key Points: Psoriatic Arthritis
(continued)

The first line of treatment is with the NSAIDS to reduce and control the inflammation [18].

Corticosteroids are used for joint injections [19].

The second-line drugs, the DMARDs, such as methotrexate are added to the treatment regime [17].

Drugs such as the TNF-alpha inhibitor are now available, for example, infliximab, etanercept, adalimumab, have significant efficacy [14] and are usually reserved for the severe cases.

Multiple Choice Questions

1. The following are true of psoriatic arthritis, except:
   A. Psoriatic nail changes are strongly associated with the development of psoriatic arthritis with DIP joint involvement.
   B. Elderly onset PsA (EOPsA) has a less severe onset and less destructive outcome than in younger subjects.
   C. The arthropathy may arise, with or after, and often as long as two decades after the onset of the skin disease.
   D. Expression of HLA-B27, HLA-DR3 or HLA-DR4 alleles portends a poor prognosis.

MCQ Answers

1 = B

Short Answer Questions

1. Name four factors which portend a poor prognosis.

SAQ Answers

1. Strong family history
2. Early onset
3. A polyarticular or erosive
4. Females

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Spondyloarthritis

58

Contents

Abstract

Their clinical features include spinal symptoms, peripheral arthritis and enthesopathic lesions. Severe spinal disease is more often seen in males and peripheral joint involvement in females. Late-onset peripheral spondyloarthropathy (LOPS) is characterised by severe disease, markedly raised inflammatory markers, oligoarthritis and oedema of the extremities, and HLA-B27 is positive. Late-onset psoriatic spondyloarthropathy shares a number of characteristics with late-onset spondyloarthropathy not seen in spondyloarthropathy patients of younger onset.

Keywords

Spondyloarthropathy · Late-onset peripheral spondyloarthropathy · Late-onset psoriatic spondyloarthropathy · Enthesopathic lesions

Introduction

Spondyloarthritis (SpA) comprises a group of diseases that share a common clinical and radiological characteristics [1] and includes ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis, arthritis associated with inflammatory bowel diseases and undifferentiated spondyloarthropathies [1–5]. Each subset is seen in the elderly [4]. The prevalence of late-onset spondyloarthritis is not well known [1]. In Sweden, the prevalence of spondyloarthritis resulting from a doctor consultation was similar to that of rheumatoid arthritis, and men were equally affected as women [6]. AS affects more men than women and PsA was more prevalent in women [6].

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_55

Clinical Manifestations

Their clinical features include spinal symptoms, peripheral arthritis and enthesopathic lesions [1]. Severe spinal disease is more often seen in males and peripheral joint involvement in females [7]. Ankylosing spondylitis (AS) is not common after the age of 50 years [8, 9]. Patients with late-onset SpA have systemic symptoms, more severe cervical [10] and lumbar pain and inflamed peripheral joint involvement [10] and aseptic osteitis compared to early-onset ankylosing spondylitis (AS) [11]. Dactylitis, enthesopathy [10] or uveitis may occur [12].

Late-onset peripheral spondyloarthropathy (LOPS) is characterised by severe disease, markedly raised inflammatory markers, oligoarthritis and oedema of the extremities [4], and HLA-B27 is positive [13].

Undifferentiated spondyloarthritis (uSPA) is relatively more frequent than late-onset AS [11, 14, 15]. Its clinical features are very similar to that seen in the young and middle-aged adults but for the occurrence of swelling and pitting oedema of the extremities [15].

Reactive arthritis and enthesopathic arthritis rarely occur in the elderly [4].

Late-onset psoriatic spondyloarthropathy shares a number of characteristics with late-onset spondyloarthropathy not seen in spondyloarthropathy patients of younger onset [10, 11].

Diagnosis

The Assessment of SpondyloArthritis International Society (ASAS) has developed new criteria for axial or peripheral SpA [16–18] that allows the identification of patients under the age of 45 years at the time of onset [18]. Sacroiliitis on MRI and HLA-27 has significant roles [17] and is included in the criteria [18].

The diagnosis of late-onset uSPA may not be difficult when the patients present with two or more clinical features of SpA, a family history and/or B27 antigen and fulfil the Amor criteria [15]. When the patient with SpA presents with oedema of the extremities, the differential diagnosis will include RS3PE syndrome, polymyalgia rheumatica [19], giant cell arteritis [20] and other inflammatory conditions in which remitting distal extremity swelling has been observed [15]. These include SLA, Sjorgen's syndrome, systemic sclerosis and dermatomyositis, among others [15].

Magnetic resonance imaging (MRI) is increasingly used for the early recognition of sacroiliitis or spinal inflammation in SpA [17]. In enthesitis and peripheral synovitis, Doppler ultrasonography is useful [14].

Treatment

The main aim of treatment is to improve patient outcomes and long-term QoL [18]. The elderly, apart from certain adjustments, are treated similarly to younger patients [18]. The treatment includes NSAIDs and local and systemic corticosteroids. Disease-controlling drugs such as sulphasalazine and methotrexate have not been proven to be very effective [4].Tumour necrosis factor-alpha blocking agents could be used in selected cases [15] but have not been specifically tested in the elderly [4]. There is only one clinical trial in the elderly population aged over 65 years and over with AS [21] and are associated with increased risk of infection [18] or worsening of heart failure [4].

Impact

The effects of AS vary from individual to individual; about half are severely affected, whilst others have only few symptoms [22]. It has been reported that the unemployment rates are three times that seen in the general population [23]. Persistent pain and fatigue are problems from the patient's perspective; as a result, health-related quality of life is significantly impaired (Box 1).

Box 1 Key Points: Spondyloarthritis

Their clinical features include spinal symptoms, peripheral arthritis and enthesopathic lesions [1].

Severe spinal disease is more often seen in males and peripheral joint involvement in females [7].

Patients with late-onset SpA have systemic symptoms, more severe cervical [10] and lumbar pain and inflamed peripheral joint involvement [10] and aseptic osteitis compared to early-onset ankylosing spondylitis (AS).

Late-onset peripheral spondyloarthropathy (LOPS) is characterised by severe disease, markedly raised inflammatory markers, oligoarthritis and oedema of the extremities [4], and HLA-B27 is positive [13].

The main aim of treatment is to improve patient outcomes and long-term QoL [18].

Multiple Choice Questions

1. The following are true of spondyloarthropathy, except:
   A. Clinical features include spinal symptoms, peripheral arthritis and enthesopathic lesions.
   B. Late-onset peripheral spondyloarthropathy (LOPS) is characterised by mild disease.
   C. Late-onset psoriatic spondyloarthropathy shares a number of characteristics with late-onset spondyloarthropathy.
   D. Shares common clinical and radiological characteristics with ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis and arthritis associated with inflammatory bowel diseases.

MCQ Answers

1 = B

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Osteoarthritis

59

Contents

Abstract

Osteoarthritis (OA) is the most common age-related joint disease throughout the world and symptomatic OA is a leading cause of disability among elders. Currently, there is increasing realization that OA affects all the joint tissues. These include the synovium, meniscal pathology, bone marrow lesions, and subchondral bone. OA was thought to be a noninflammatory condition, but now it is evident that this is not so and there is evidence linking local inflammation with pain measured as synovitis/effusion. The present review will highlight the causation and pathogenesis of the disease.

Keywords

Osteoarthritis · Cartilage · Bone marrow lesions · Meniscal pathology · Rhizarthrosis · Secondary osteoarthritis

Introduction

It is classified as primary or idiopathic and secondary to some known cause. The incidence may vary depending on the criteria used, clinical or radiological. In a study of OA in the elderly, although there was correlation between clinical and radiological evidence, often clinical signs were present without radiological evidence. On the other hand, moderate to severe radiological changes were present without clinical signs [1]. OA is the most common age-related joint disease in the United States and throughout the world [2], and symptomatic OA is a leading cause of disability among elders. With a growing elderly population, the socioeconomic burden of this disease is substantial. Prevalence increases in 10% of men and 20% of women between ages 45 and 60 years and to more than 50% in women over the age of 85 years [3]. About 15% of Australians

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_58

have self-reported arthritis (about 3 million) andOA accounts for most of them [4, 5]. OA results when the cartilage breakdown exceeds cartilage synthesis. The cartilage has been the focus of research into the pathophysiology of osteoarthritis, but currently there is increasing realization that OA affects all the joint tissues [6]. These include the synovium [6, 7], meniscal pathology [8], bone marrow lesions [9], and subchondral bone.

MRI-based studies have significantly improved our understanding of the pathogenesis of OA. In the pathogenesis of OA, there has been considerable interest in the role of bone [10], and bone marrow lesions (BML) are an important source of OA symptoms and implicated in the causation and pathogenesis of the disease [11, 12, 13]. Several bone tissue abnormalities such as bone marrow necrosis and fibrosis together with necrotic and remodeled trabeculae are included with BMLs [9] and histologically microfracture or bone damage [14]. Furthermore, bone mineral density (BMD) is significantly increased with BML locations. [15]. BMLs are associated with pain [11, 15, 16, 17], malalignment [18], predicting progression on radiographs [18, 19], compartment-specific joint space degeneration [15, 18, 20] and predictive of cartilage loss [12, 21]. On T2-weighted fat-suppressed images, they are detected as high intensity regions [15]. Individuals with a very high risk for compartment-specific OA progression can be identified using BML lesions on MRI [22].

OA was thought to be a noninflammatory condition but now it is evident that this is not so [8], and there is evidence linking local inflammation with pain measured as synovitis/effusion [23]. The histological changes in the synovium in OA is suggestive of an "inflammatory" synovitis, and the synovial reaction can result in formation and release of cytokines and chemokines [6] causing joint damage through alarmins [7]. Distinct risk factors such as age, obesity, and joint injury associated with definite subsets of OA operated through specific pathogenic pathways are being considered by researchers [7].

Clinical Manifestations

OA can be divided into two types, primary and secondary (Fig. 1) In the early stages OA is asymptomatic. The nodal form presents as Herbeden's and Bouchard's nodes in the distal and proximal interphalangeal joints. The first carpometacarpal phalangeal and first metatarsal phalangeal joints are primarily involved. A subset of primary osteoarthritis is erosive inflammatory OA characterized by rapid destructive OA of the shoulders and less often knees in the elderly. It is painful and is associated with osteoporosis of the hands and erosions. Destructive lesions in some of the distal and or proximal interphalangeal joints are an erosive form of synovitis and often confused with rheumatoid arthritis, as patients have inflammation of the interphalangeal joints with erosive changes. The absence of signs and symptoms in the wrist and metacarpophalangeal joints should exclude RA and confirmed by a negative rheumatoid factor/anti-CCP antibodies. Secondary OA is commonly related to trauma and involves the hips, knees, and spine (Box 1).

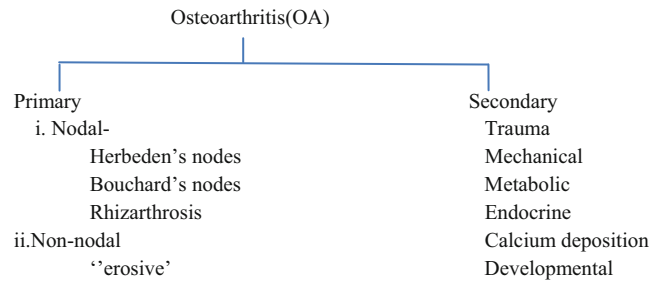

Fig. 1 Primary and secondary osteoarthritis

Box 1 Clinical Features of Osteoarthritis
Joint pain and/or tenderness
Morning stiffness
Joint swelling and or bony swelling
"Gelling" post exercise
Crepitus
Muscle wasting and or weakness
Limitation of range of movements and or function
Effusion and or warmth
Deformity and or instability

Nodal and Generalized Osteoarthritis

Primary osteoarthrosis mainly affects women in their menopause and involves numerous finger joints of the hand, and apart from involvement of the distal interphalangeal joints (Heberden's nodes) and the proximal interphalangeal joints (Bourchard's nodes), other joints may be affected like the metacarpophalangeal of the fingers and often the carpometacarpal joint of the thumb and the joint surfaces of the trapezium. Involvement of the carpometacarpal joint of the thumb (Fig. 2) gives rise to restricted joint movement with compensatory hyperextensibility of the metacarpophalangeal joint. There is also a subluxation at the carpometacarpal joint causing the metacarpal bone to protrude outwards. With disease progression the abductors of the thumb atrophy, resulting in adduction contracture. All three changes constitute what is termed "rhizarthrosis." Rhizarthrosis may seriously affect the functioning of the thumb but also the hand as a whole [24]. In a study of 1041 subjects aged 71–100 years, 30% of whom were men, the prevalence of symptomatic hand OA was higher in women (26.2%) then in men (!3.4%). Symptomatic hand OA is common among the elders and impairs hand function [25]. There is no correlation between pain and radiological or pathological evidence of disease [26]. The other joints predominantly involved are the weight bearing joints, the hips, and knees. Patients mostly feel stiffness and pain and is relieved by rest and may "lock" or "give way" as of internal damage to the cartilage.

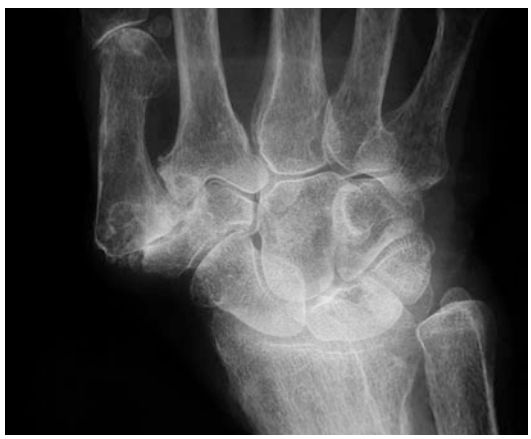

Fig. 2 Osteoarthosis of the first metacarpocarpal joint (Reproduced, with kind permission, from Prof. Nicholas Manolios)

Diagnosis

The diagnosis is based on clinical and radiological examination with normal levels of inflammatory markers and negative RF and anti-CCP. The classic triad of findings on X-ray are sclerosis, narrowing of the joint space, and osteophytes (Fig. 3). All

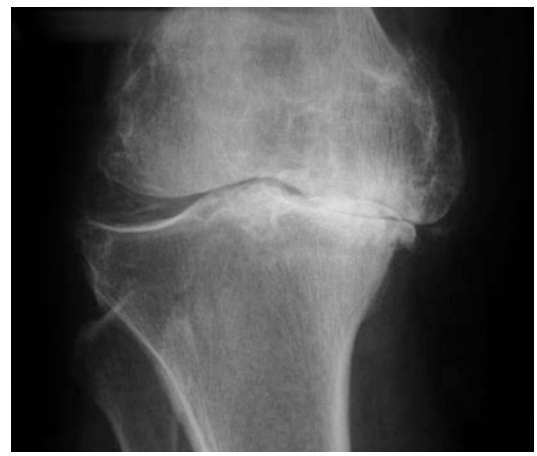

Fig. 3 X-ray changes in osteoarthritis of the knee showing narrowing of the joint space, sclerosis, and osteophyte formation (Reproduced, with kind permission, from Prof. Nicholas Manolios)

three must be present to make a firm diagnosis. Osteophytes are the most specific and joint space narrowing the least. More recently radiographs with varying degrees of flexion of the knee and X-ray beam angles have improved intra-articular visualization in knee OA [27]. Recently, OA diagnosis has been improved with additional modalities such as MRI, US, and OCT (optical coherence tomography) [27]. In knee OA, MRI visualizes most components of the joint including articular cartilage, synovium, bone marrow, intra-articular ligaments, and subchondral cysts which are not detectable by plain X-rays [28].

Management

There is no cure for OA. The aim of treatment of osteoarthritis is minimizing pain and improving joint movement. Treatment becomes more complicated with advancing age. Pain in OA predisposes to restricted movement, reduced physical activity, restrained social activity, and work capacity begetting emotional stress [29]. It has been shown that elderly patients with OA benefit considerably by treatment involving them in self-management, occupational therapy, medications (simple analgesics rather than NSAIDS or COX IIs are recommended for pain relief), and surgery to reduce pain and thereby maintain or improve joint mobility and functional ability [29].

Our understanding of the pathogenesis of osteoarthritis has improved with the development of newer imaging techniques including magnetic resonance (MRI), ultrasound (US), and optical coherence tomography (OCT). OA affects all of the joint tissues [6]. In knee OA, the MRI can provide direct visualization of the knee structures, including cartilage defects, inflammatory synovitis [6], and bone lesions such as bone marrow lesions, bone mineral density, and subchondral bone size [21]. According to Jones [8], classifying patients on their pathology in knee OA enables a more personalized medicine approach, for example, if there is effusion/synovitis – anti-inflammatory therapy; if there is BML, zoledronic acid may help, and there is indication in support of statins and bisphosphonates for improving RA disease activity and preventing erosions [30].

Glucosamine and chondroitin are being used as therapeutic agents for symptoms of osteoarthritis. However, they are classified as dietary supplements. Their effectiveness continues to be debated. In order to determine their efficacy, a randomized double-blind placebo and active comparator (celecoxib) controlled trial, the Glucosamine-Chondroitin Arthritis Intervention Trial (GAIT) of 1583 patients with symptomatic osteoarthritis (knee), was conducted. The findings were celecoxib had statistically significant pain relief versus placebo, and about 70% taking celecoxib had a 20% or greater reduction in pain versus 60% of placebo [31]. For a subset of patients with moderate to severe pain glucosamine with chondroitin sulfate provided significant pain relief versus placebo. About 70% had 20% or greater pain relief versus 54% for placebo. It was also noted that taking chondroitin sulfate had statistically significant improvement in the knee swelling [32]. In a subset of patients with mild osteoarthritis of the knee, glucosamine and chondroitin sulfate alone or in combination did not reduce pain significantly [33]. Based on the results of recent randomized controlled trials and meta-analysis it was concluded that chondroitin sulfate and glucosamine provided small to moderate symptomatic effectiveness in osteoarthritis [34]. There is also some evidence to suggest a structure modifying effect of glucosamine and chondrotin sulfate [34].

Impact

OA is the most common form of arthritis and is a serious disease [35]. It is the pain in OA that limits the quality of life [36]. The best estimates of the United States prevalence and number of individuals afflicted with OA in 2005 was 20 million [37]. The impact of OA is worsened by the presence of comorbidities including cardiovascular diseases, hypertension, diabetes, respiratory disease, and renal disease [38, 39]. Furthermore, OA increases the risk of developing cardiovascular disease, hypertension, renal impairment, and diabetes. The pain in OA results in functional

impairment and emotional well-being [40, 41]. Patients with arthritis have difficulty in physical function (walking, stooping, reaching), in personal care, and household care [42]. The limitations imposed by OA results in loss of self-esteem, self-image, and can lead to negative emotional states [43, 44], anxiety, and depression. QOL of patients with OA with or without comorbidities was significantly poorer than their healthy counterparts, particularly in the domains of not only physical status but also social functions and general health [45] (Box 2).

Box 2 Key Points: Osteoarthritis

OA is the most common age-related joint disease worldwide [2].

Primary OA mainly affects women in their menopause and involves numerous finger joints.

OA is characterized by an imbalance between extracellular matrix biosynthesis and extracellular matrix degradation at the molecular level and the articular cartilage is the primary site of tissue injury response [6].

Symptomatic hand OA is common among the elders and impairs hand function [8].

Based on the results of recent randomized controlled trials and meta-analysis, it was concluded that chondroitin sulfate and glucosamine provided small to moderate symptomatic effectiveness in osteoarthritis [14].

Elderly patients with OA benefit by treatment involving them in self-monitoring, occupational therapy, medications (simple analgesics), and surgery to reduce pain.

Multiple Choice Questions

1. The following are true of osteoarthritis, EXCEPT:
   A. Prevalence increases in 10% of men and 20% of women between 45 and 60 years to more than 50% in women over the age of 85 years.
   B. A subset of OA is erosive inflammatory OA characterized by rapid destruction of shoulders less often knees in the elderly.
   C. Symptomatic hands OA is common in the elderly but does not impair hand function.
   D. The term rhizoarthrosis constitutes – hyperextensibility of the first MCP joint, subluxation with protrusion of the MCP outwards, and atrophy of the abductors of the thumb resulting in adduction of the thumb.

MCQ Answers

1 = C

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Crystal-Induced Arthritis

60

Contents

Abstract

The incidence of gout seems to be rising in the elderly, both in men and women in countries where the life expectancy is lengthening and the frequency of overuse of diuretics. Gout predominantly affects the middle ages and elderly people and rarely occurs in young adult or children. CPPD crystal deposition disease is the second most common form of crystal-induced arthritis and is common in the elderly. The chapter discusses the pathogenesis of gout and clinical management.

Keywords

Gout · Crystal-induced arthritis · Elderly-onset gout · Hyperuricemia · CPPD crystal deposition disease

Gout

Introduction

Gout accounts for millions of outpatient visits annually and its prevalence is increasing [1] and is the most common inflammatory arthropathy in men. Gout occurs in two forms: classical gout presenting in middle age and elderly-onset gout (EOG), and because of its atypical presentation it is often seen to be a separate entity and has been confirmed as the most common inflammatory arthropathy [2]. The former has its highest incidence in males and men predominate in the ratio of 2:1 with females. EOG has however a more equal gender distribution [3] and women tend to develop gout at more advanced stage of life particularly after menopause. The

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_57

incidence seems to be rising in the elderly, both in men and women in countries where the life expectancy is lengthening and the frequency of overuse of diuretics has increased [4, 5]. The prevalence increases with age reaching 9% in men and 6% in women older than 81 years of age [6]. It often remains misdiagnosed or the diagnosis is delayed despite the high prevalence [2]. In the United Kingdom, the prevalence of gout was reported as 1.4% in 1999 and as high as 7% in men older than 65 years in a study examining the epidemiology [7]. Gout predominantly affects the middle ages and elderly people rarely occurring in young adult or children. According to Japanese researchers, there is now evidence that more people are developing gout before the age of 30 [8], and the early onset gout is associated with dysfunction of ABCG2/BCRP gene. ABCG2 gene is said to transport urate.

Interleukin 1beta(IL-1beta) is the driving force in the pathogenesis of gouty arthritis [9, 10]. Neutrophil activation is brought about by IL-1beta together with pro-inflammatory cytokines, Il-8, TNF alpha [11, 12]. The cytokines are activated by caspases which are in turn regulated by inflammasome which is the sensor of inflammatory stimuli [13]. The monosodium urate (MSU) crystals activate NALP3 inflammasome increasing the production of IL-1 and the inflammatory state [14]. The MSU crystals also interact with the lipid membranes through cell membrane activating several signal transduction pathways promoting neutrophil accumulation [15] and neutrophil apoptosis is essential for resolution [15]. Greater understanding of pathophysiology of gout resulted from genetic advances with identification of URAT-1 transporter [11] located at the apical brush border of the proximal nephron and associated with reduced urate excretion and hyperuricemia [16]. The inheritance of the genetic variation in SLC2A9 [11] identified as an additional urate transporter increases the risk of developing gout [17]. IL-1beta has also been implicated in bone destruction and erosions in other inflammatory arthritides [9]. It has also been suggested that MSU deposition is associated with underlying osteoarthritis and osteoclasts, and the receptor

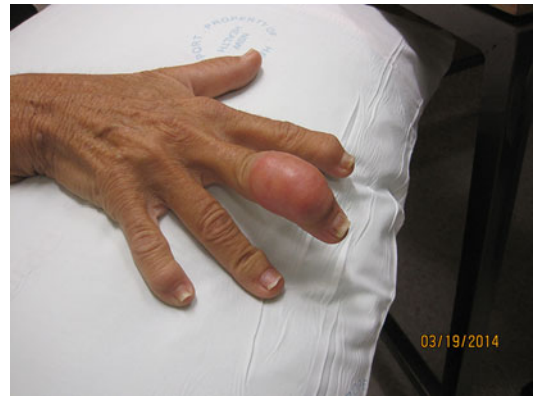


Fig. 1 Gout tophus (Reproduced, with kind permission, from Prof. Nicholas Manolios)

for activation of nuclear factor *k*B (RANK) and the RANK ligand (RANK-RANKL) pathway have important roles in the pathogenesis of bone lesions in gout [9]. Figures 1 and 2 show the pathology in chronic gout.

Clinical Manifestations

The pattern of joint involvement is of value in establishing a specific diagnosis. Monoarthritis is the most common presentation in the middle age onset gout. It has a predilection to involve the larger peripheral joints in the lower extremities [1]. The common site of initial involvement in acute gout (podagra) is the first metatarsophalangeal joint of the foot. The clinical picture has changed in that the disease is polyarticular, patients older and often associated with renal insufficiency and cardiovascular diseases [18]. Often symptoms such as pain and signs of inflammation occur within minutes to hours. Typically the patient retires well and is awakened from sleep with severe pain that precludes weight bearing. An acute attack is often related to some precipitating event such as excessive alcohol ingestion, postsurgical operation, or injury. Gout presents differently in the elderly and has more equal gender distribution [6]. In the elderly, it is often a chronic polyarthritis [3]

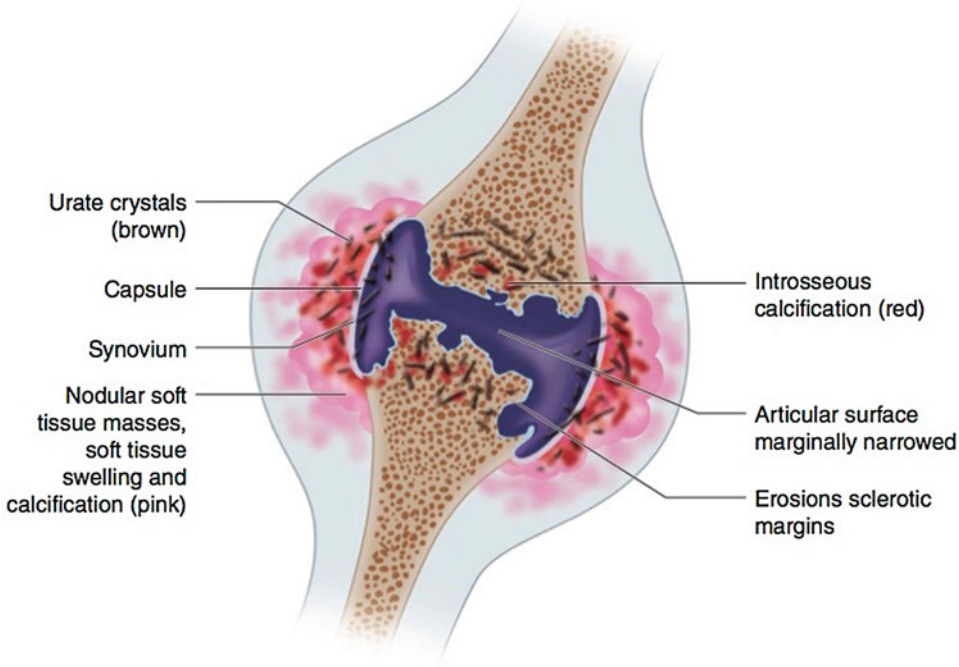


Fig. 2 Schematic diagram shows the pathology of chronic gout. (Para-articular soft tissue swelling, punched out articular, para-articular and extra marginal erosions, and calcification of tophi (MSU crystals surrounded by granulomatous tissue)

sometimes with minimal inflammation. In about 25% of elderly women, multiple small joints of the hands are affected [19]. There is a proclivity for urate crystals to be deposited in osteoarthritic joints [9, 20] (Table 1).

Gout occurs in four stages (i) hyperuricemia, (ii) acute, (iii) intercritical, and (iv) chronic [21]. In hyperuricemia, the serum urate levels rise above 7 mg/dl. In chronic gout, there are persistently painful joints with urate deposits in the cartilage between bones, tendons, and soft tissue. The skin over the deposits develops sores and may ulcerate and exude white pus [22]. When the unic acid level in blood is high and urate crystals are present in the joint fluid, usually X-ray shows damage to cartilage and bone (Fig. 3). In intercritical gout, between gout episodes there are symptom-free intervals. Many after the first attack have a second between 6 months and 2 years, while for others the attacks are always mild and infrequent [23].

Diagnosis

The diagnosis of gout is confirmed by demonstration of negatively birefringent, needle-shaped MSU crystals in synovial fluid by using polarized light microscopy [24]. Plain X-rays are not very helpful other than in the early stages showing soft tissue swelling, however is helpful in revealing erosions in chronic gout [25]. With the advent of new imaging techniques, joint damage and tophi can be demonstrated at an earlier stage [25]. These include ultrasound (US), CT scan, Dual-energy CT (DECT), and MRI. US is being used increasingly in gout and can benefit in the diagnosis [26] and shows the inflammatory aspects of gout including synovitis, tenosynovitis, and soft tissue inflammation [25]. Descriptions of gout with US include "hyperechospots" and "snow storm appearance" which are believed to be due to echoes produced by MSU crystals [27]. The double contour sign has a specificity of 97.3% for the detection of gout [28].

Table 1 Differences between elderly-onset gout and classical gout

	Elderly-onset gout	Classical gout
Age (years)	65 and over	65 and under
Gender ratio (M:F)	1:1	2:1
Mode of onset	Subacute/chronic	Acute, pain, swelling, erythema
Pattern of joint involvement	Polyarticular-joints of the upper extremities	Typically monoarticular joints of the lower extremities
Tophi	Increased incidence localization on OA nodes	
Course	Fewer acute episodes Chronic, indolent	Frequent acute episodes
Associated factors	Diuretic use	
	Hypertension	
	Renal impairment	
	Low dose aspirin	
	Alcohol abuse	

Information sources: De Leonardis et al. [2], Fam [3]

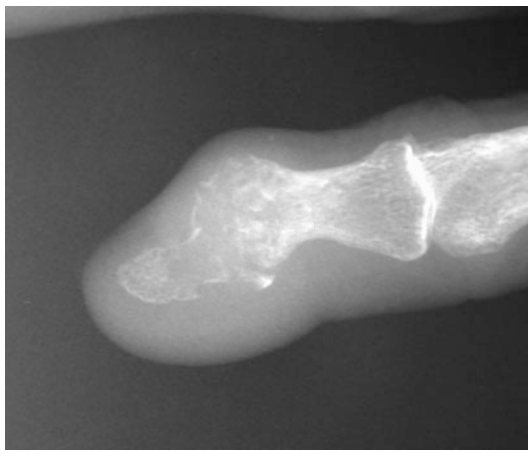


Fig. 3 X-ray changes in severe gout-marked destructive changes at the distal intertarsal joint of the big toe (Reproduced, with kind permission, from Prof. Nicholas Manolios)

Subclinical gout can be identified with high specificity with DECT in the detection of MSU crystal in soft tissues, tendons, and ligaments [29].

Treatment

It is important to begin therapy as early as possible and maintain a negative uric acid balance for many years. Objectives of treatment include (i) termination of the acute attack, (ii) prevention of acute flares, and (iii) prevention of complications associated with deposition of urate crystals in tissues [30]. The main aim is to relieve articular symptoms and reduce hyperuricemia [31].

An episode of gout can be precipitated by overindulgence in alcohol, eating wrong foods (see Box 1), injury to joint, severe illness, surgery, and chemotherapy. The use of topical ice and rest of the inflamed joint in an acute gouty attack are useful [30]. Acute attacks could be terminated by the use of nonsteroidal anti-inflammatory agents and oral and intraarticular injections of corticosteroids which is the first-line therapy depending on comorbidities, and colchicine is second-line therapy [2]. The NSAIDs are not recommended in patients with peptic ulcer, renal failure, cardiac failure, or uncontrolled hypertension. Systemic and intraarticular corticosteroids are increasingly being used for treating acute gouty flares in aged patients with medical disorders contraindicating the use of NSAIDs [3]. Long-term use should be discouraged because of the severe long-term effects. Although there are no randomized trials to uphold the use of intra-articular corticosteroids in acute gout [32], their beneficial effect in rheumatoid arthritis and osteoarthritis can be generalized its use in acute gout. It may be useful when NSADs and colchicine are contraindicated [32]. For the knee joint, 5.7 mg of betamethasone or 40 mg of methylprednisolone is recommended [33]. It has been observed that dosing is based on the size of the involved joint [34]. ACTH is effective and safe for treatment of gout in hospitalized patients [35].

In those with renal impairment, low-dose colchicine has been suggested for acute gouty arthritis [36]. Colchicine is poorly tolerated in the elderly and best avoided [3]. There should be a long-term reduction of serum uric acid in the treatment of chronic gout. Patients with renal calculi, renal insufficiency, concomitant diuretic therapy, and urate overproduction should be

treated with xanthine oxidase inhibitors such as allopurinol, oxipurinol, and febuxostat as first-line treatment [30]. Febuxostat is a nonpurine selective inhibitor of xanthine oxidase and excreted by the liver and does not require dose adjustment in patients with mild and moderate renal impairment [37]. Pegloticase, a polyethylene glycol-conjugated uricase, is another powerful hypouricemic drug [37, 38] and is used in refractory gout [38]. In allopurinol-allergic patients and under excretors with normal renal function, uricosuric drugs such as probenecid, benzbromarone, and losartan should be used [10]. More recently several biological drugs targeting particular points in gout target mainly interluekin-1 beta and urate synthesis acting as symptom relievers, and urate-lowering therapies may improve patients' prognosis [31]. Supplemental vitamin C (500–1000 mg/daily) may be beneficial in lowering serum uric acid levels [39].

Treatment is usually not required for hyperuricemia (>7 mg/dl) in the absence of gout. Treatment is indicated for those with urolithiasis, gout with elevated serum urate (9.0 mg/dl), tophaceous gout, where there is a contraindication for the use of drugs such as corticosteroids and NSAIDs to treat acute attacks, and in those with severe or frequent attacks in spite of prophylactic NSAIDs, colchicine, or both (Tables 2 and 3; Algorithm 1).

Impact

Chronic gout can affect every aspect of daily life. It can have a profound impact and cause numerous consequences for the both patient and the family [46] with dependency on family and others [47]. Depending on the severity, it can interfere with several basic functions such as walking and self-care. It affects the emotional and psychological well-being. Psychological distress can lead to anxiety, depression, and reduced social interactions and community participation. Men with gout experience shame, embarrassment, and stigma which leads to trivialization of the impact of disease despite its severity [46]. Overall it has

Table 2 Drugs used in gout, dosing, indication, contraindications, and adverse effects

Agent	Dose	Indication	Contraindications	Adverse effects
I. NSAIDS				
Indomethacin (Indocid)	50–75 mg PO initially then 50 mg 6 h tapered in 7 days and terminated	Acute gout intercritical stage low dose NSAIDs if intolerant to colchicine	Peptic ulcer history systemic anticoagulation hypersensitivity, acute asthmatic attacks provoked by aspirin or other NSAIDs	Gastric irritation, ulceration perforation, hemorrhage, fluid retention, nephropathy, elevation of blood pressure liver dysfunction
II. Corticosteroids				
Prednisolone ORAL	0.5 mg/kg/day taper by 5 mg each day	Acute gout		Fluid retention, impaired wound
Intra-articular INJECTION	Small joints 5–20 mg Large joints 10–40 mg	Acute gout		
ACTH	40–80 U IM repeat 8 hourly as necessary	Acute gout		Stimulation of mineralocorticoid release may cause fluid overload
III. Colchicine	0.6 mg PO q 1 h to total dose of 4–5 mg or until diarrhea and vomiting occurs	Acute gout	Poorly tolerated in the elderly severe renal and liver impairment, blood dyscrasias, serious cardiac and GI disorders, hypersensitivity	Blood dyscrasias-fatal gastro-intestinal, myoneuropathy, eye disorders vascular damage

Information sources: Wechalekar et al. [32], McGill [33], Khanna et al. [34], Globalrph [40]

Table 3 Urate lowering drugs for treatment of gout and hyperuricemia

Drug	Dosage	Indication	Contraindication	Adverse effects
I. Inhibits uric acid synthesis				
Allopurinol (Zyloprim)	Begin 50–100 mg daily increase till serum urate <6 mg per dl	Chronic tophaceous and erosive gouty arthritis secondary hyperuricemia	Hypersensitivity[a]	Rash, urticaria, gastro-intestinal headache, fatal hypersensitivity syndrome (in patients taking thiazide concomitantly or renal insufficiency, interstitial nephritis
Febuxostat (Uloric)	40 mg or 80 mg once daily	Hyperuricemia gout flares	Asymptomatic hyperuricemia	Liver functional abnormalities
Pegloticase (Krystexxa)	8 mg as IV every 2 weeks	Refractory gout	Asymptomatic hyperuricemia	Anaphylaxis, infusion reactions, gout flares, Congestive heart failure.
II. Increasing excretion of uric acid				
Probenecid (Benemid)	Begin 250 mg bd increase till serum urate <6 mg per dl to allopurinol maximum dose 3 g per day	Recurring gout who are allergic or intolerant	Hypersensitivity urolithiasis, renal calculi	Hypersensitivity dizziness, headache, may precipitate gouty attack
Sulfinpyrazone (Anturan)	Start 50 mg tds increase till <6 mg per dl maximum dose 800 mg/day	Recurrent gout chronic gout serum urate	Acute attacks of gout, peptic ulcers	GI upsets; skin reactions blood dyscrasias, jaundice, hepatitis

Information sources: Globalrph [40], Avena-Woods and Hilas [41], medsape.com/drug/krystexa-peglotiase-999601 [42], www.drugs.com/dosage/flexostat.tml [43], www.medicines.org.uk/emc/medicie/26935 [44]
[a]In patients with high risk of allopurinol hypersensitivity to screen for HLA-B*5801 [45]

an intense impact on the quality of life [47–49]. They can experience intense pain during an acute attack which can have an impact on patient's physical and emotional health and reduced recreational and social participation [50, 51]. A significant increase in functional impairment and morbidity occurs in many patients with gout due to the presence of comorbidities such as cardiovascular diseases, obesity, diabetes, and renal disease [52] (Box 2).

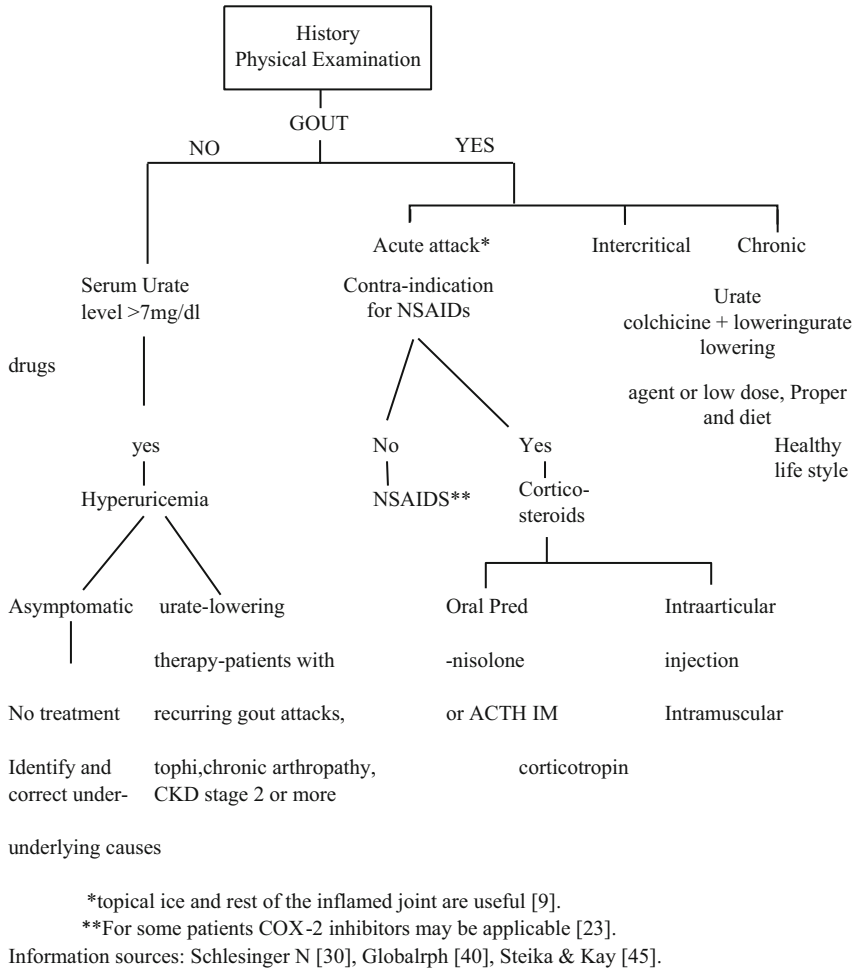
Calcium Pyrophosphate Dihydrate (CPPD) Crystal Deposition Disease: "Pseudo-gout"

Introduction

CPPD crystal deposition disease is a degenerative arthropathy with deposition of calcium pyrophosphate dehydrate crystals in the joints, fibrocartilage, bursae, capsules, ligaments, and tendons, which presents with variable manifestations and intermittent attacks of acute arthritis which may be severe or asymptomatic. The term "pseudo-gout" refers to the clinical syndrome of one or more acute or subacute attacks of self-limiting inflammation caused by crystal deposition and synovitis. It is the second most common form of crystal-induced arthritis. It is common in the elderly [52] and its prevalence increases with age, i.e., 30–50% in the 85 years and over. Both genders are equally affected.

Clinical Manifestations

The Symptom may be acute or subacute involving usually the knee or any of the larger peripheral joints. Other common presentations include calcification of the ligamentum flavum, atypical calcified tophus, erosive calcification, and spinal cord compression by intrathecal masses [53]. In most



*topical ice and rest of the inflamed joint are useful [9].
**For some patients COX-2 inhibitors may be applicable [23].
Information sources: Schlesinger N [30], Globalrph [40], Steika & Kay [45].

Algorithm 1 Algorithm for treatment of gout

cases it is asymptomatic. It is usually symptomatic in persons over the age of 60 years.

Treatment

Treatment for the attacks resembles the therapy of acute gout, and in cases of secondary forms such as haemochromatosis, hypothyroidism, hyperparathyroidism causal therapy is conceivable [54] (Boxes 3, 4).

Multiple Choice Questions

1. The following are true of gout in the elderly, EXCEPT:
   A. Increasing incidence is in part due to frequency of overuse of diuretics.
   B. In the elderly gout presents as chronic polyarthritis.
   C. Elderly-onset gout has the predominance of women.
   D. An episode of gout can be precipitated by alcohol or wrong foods.
2. The following are true in the management of gout in the elderly, EXCEPT:
   A. Colchicine is well tolerated by the elderly.
   B. Long term use of corticosteroids should be discouraged.
   C. Treatment is not required for hyperuricemia (<0.42 mm/L) in the absence of gout.

D. Systemic and intraarticular corticosteroids are increasingly being used to treat acute gouty flares in aged patients.

MCQ Answers

1 = C; 2 = A

Short Answer Questions

1. List four conditions associated with pseudo-gout (CPPD)

SAQ Answers

1. Primary hyperparathyroidism
2. Haemochromatosis
3. Hypothyroidism
4. Chronic g

Box 1 Proper Diet

Avoid or restrain food high in purine anchovies, brain, liver, kidney, tripe, sweetbread, tongue, sardines, shellfish (mussels, oysters), crab, scallop, codfish, trout fish roe, veal, venison, peas, beans, lentils, excessive red meat, and alcoholic beverages.

Box 2 Key Points. Gout

Gout is caused by monosodium urate crystal deposition in the tissues including the synovium.

Gout occurs in two forms: classical gout presenting in middle age and elderly-onset gout (EOG) and because of its atypical presentation is often seen to be a separate entity and has been confirmed as the most common inflammatory arthropathy [2].

Late onset has an atypical presentation and has equal gender distribution [3].

Incidence increasing not only to increasing life expectancy and frequency of overuse of diuretics.

In the elderly it is often a chronic polyarthritis [18].

Box 2 Key Points. Gout (continued)

In 25% of elderly women multiple small joints of the hands are affected.

Important to begin treatment as early as possible and maintain a negative balance for years.

Box 3 Some Conditions Associated with CPPD

Primary hyperparathyroidism
Haemochromatosis
Hypothyroidism
Hypomagnesaemia
Chronic gout
Postmeniscectomy

Box 4 Key Points. "Pseudo-gout"

CPPD crystal deposition disease, a degenerative arthropathy with deposition of calcium pyrophosphate dehydrate crystals in the joints.

CPPD is common in the elderly and increases with age rising to 30–50% in the over 85 years and over.

Symptoms may be acute or subacute involving usually the knee or any large peripheral joints.

Treatment for the attacks resembles the -therapy of acute gout and in cases of secondary forms such as haemochromatosis, hypothyroidism, hyperparathyroidism causal therapy is conceivable.

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Part XIII

Vasculitis in the Elderly

Part XIII provides an overview of vasculitis, the prevalence and mechanisms followed by the clinical management. The incidence of vasculitis is increasing. Of the specific vasculitis, giant cell arteritis of the elderly is the commonest. A useful classification is one based on the size of the vessel namely small vessel, small to medium size, and medium to large vessel size affected although overlap is common. The terms for Wegener's granulomatosis, Churg-Strauss syndrome, and Henoch-Scholein purpure are changed to granulomatosis with polyangitis (GPA), eosinohilic granulomatosis with polyangitis (EGPA) and IgA vasculitis for Wegener's granulomatosis, Churg-Strauss and Henoch-Scholein, respectively. There are several mechanisms involved in the vascular inflammation, namely immune complex disease, antibody-mediated disease, antibody-dependent cellular cytotoxicity, and endothelial activation, among others. Vasculitis may be primary or secondary. Any part of the body could be affected. The treatment will be very much determined by a careful evaluation, the cause, and the extent and severity of the disease. In the very elderly, vasculitic syndromes have a bad prognosis, majority deteriorating suddenly leading to death or severe functional impairment.

Vasculitis in Geriatric Patients

61

Contents

Abstract

The chapter provides an overview of vasculitis, the prevalence, and mechanisms followed by the clinical management. The incidence of vasculitis is increasing. Of the specific vasculitis, giant cell arteritis of the elderly is the commonest. A useful classification is one based on the size of the vessel, namely, small vessel, small-medium size, and medium to large vessel size affected, although overlap is common. The terms for Wegener's granulomatosis, Churg-Strauss syndrome, and Henoch-Scholein purpura are changed to granulomatosis with polyangitis (GPA), eosinophilic granulomatosis with polyangitis (EGPA), and IgA vasculitis for Wegener's granulomatosis, Churg-Strauss, and Henoch-Scholein, respectively. There are several mechanisms involved in the vascular inflammation, namely, immune complex disease, antibody-mediated disease, antibody-dependent cellular cytotoxicity, and endothelial activation, among others. Vasculitis may be primary or secondary. Any part of the body could be affected. The treatment will be very much determined by a careful evaluation, the cause, the extent, and severity of the disease. In the very elderly, vasculitic syndromes have a bad prognosis, majority deteriorating suddenly leading to death or severe functional impairment.

Keywords

Vasculitis · Primary secondary vasculitis · International Chapel Hill Consensus Conference (CHCC) · ANCA associated vasculitides · Giant cell arteritis

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_61

Introduction

The frequency of vasculitis varies among different geographic regions. An annual incidence and prevalence were found to increase in three northern counties of Norway from 5.2/million (1984–1988) to 20.0/million (1994–1998) [1]. A similar increase was seen in Sweden [2]. There is an increasing incidence of primary systemic vasculitides (PSV) with age and microscopic polyangiitis (MPA) that is more common than Wegener's granulomatosis (WG) in patients from northwest Spain [3]. ANCA vasculitis in patients over the age of 75 years or older is associated with a higher mortality and morbidity [4] causing rapid deterioration of renal function, and the elderly [5] have a greater risk of dying [6] within the first 6 months of diagnosis [7].

The detection of antineutrophil cytoplasmic autoantibodies (ANCA) has made it possible for small vessel vasculitis to be further classified, as ANCA-associated and non-ANCA-associated vasculitis [8]. However, there are several issues that have to be addressed. The second International Chapel Hill Consensus Conference (CHCC) held in 2012 revised the nomenclature reflecting on the aetiopathological and vessel size and types of inflammation [9] and included important categories not included in the 1994 CHCC [10] and in particular ANCA [10]. The terms for Wegener's granulomatosis, Churg-Strauss syndrome and Henoch-Schonlein purpura were changed to granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and IgA vasculitis, respectively. In 1990 the American College of Rheumatology (ACR) classification did not include microscopic polyangiitis (MPA) or use ANCA, and the CHCC did not include ANCA [11]. The ANCA-associated vasculitides are further categorized by necrotizing inflammation of small vessel together with ANCA directed to either proteinase 3 (PR3) or myeloperoxidase (MPO); the former (PR3ANCA) is associated with granulomatous vasculitis as in Wegener's granulomatosis [12]. The ANCA-associated vasculitides are a group of disorders which include Wegener's granulomatosis (GPA), microscopic polyangiitis (MPA) and Churg-Strauss syndrome EGPA). They are rare in childhood and peak in the 65–70-year-old age group [13].

Three immunopathological categories of vasculitis have been proposed [14]: (i) circulating anti-GBM antibodies cross reacting with alveolar basement membrane producing pulmonary renal syndromes, (ii) granular deposits of immunoglobulin and complement on vessel walls and glomeruli in small vessel vasculitis and (iii) few if any deposits are seen in the target tissues as in Churg-Strauss syndrome, Wegener's granulomatosis, microscopic polyangiitis and in renal-limited pauci-immune crescentic glomerular nephritis [14]. There are several mechanisms involved in the vascular inflammation, namely, immune complex disease [15], antibody-mediated disease [15], antibody-dependent cellular cytotoxicity and endothelial activation, among others.

Clinical Manifestations

Vasculitis may be primary or secondary [16]. In primary vasculitis, there is no known cause and the vascular system is the primary target organ. Secondary vasculitis occurs when the vascular system is injured by infection, drug or toxin (Box 1). Although more often the cause of vasculitis is not known (primary), it has many other causes such as a reaction pattern to an underlying medication, infection, malignancy or connective tissue disorders. The skin is commonly affected, and the skin manifestations may present as papules, nodules and/or urticaria, palpable purpura or widespread purpure to necrosis and ulceration [17] (Fig. 1). Infection-related vasculitis constitutes the most common cause of secondary vasculitis. Vascular damage can be caused directly or indirectly by a variety of organisms, be it viral, bacterial and fungal infections. Hepatitis B and C, HIV [18–20], EBV and organisms such as *Streptococcus*, *Staphylococcus*, *Campylobacter* [21] can cause vasculitic syndromes which are predominantly confined to the skin.

Box 1 Secondary Vasculitis

Infection-related vasculitis
Drug hypersensitivity-related vasculitis
Vasculitis secondary to connective tissue disorders
Malignancy-related vasculitis
Hypocomplementemic urticaria vasculitis
Post organ transplant vasculitis

Information source: Hom [22]

Drug-related vasculitis has variously described as necrotizing hypersensitivity or allergic angiitis or microscopic panarteritis nodosa [23]. In a study of 30 patients with drug-related vasculitis, small arteries, arterioles, capillaries and venules were involved. Histologically, the inflammatory infiltrate consisted primarily of mononuclear cells and increase in numbers of eosinophils found in all three layers of the vessels [23]. The American College of Rheumatology made a criteria for the diagnosis of hypersensitivity vasculitis (HV) [24]. They are (i) older than 16 years of age, (ii) use of a drug before onset of symptoms, (iii) skin rash and (iv) biopsy of skin rash showing neutrophils [25]. The drugs most frequently found to be associated with HV are shown in Box 2. Hydralazine and propylthiouracil have been implicated in the causal of ANCA-associated vasculitis [16], and resolution of the vasculitis is likely to occur after withdrawal of the offending agent [26]. The major symptoms apart from the skin rash are joint pains and enlargement of lymph nodes. The symptoms usually appear 7–10 days after exposure to the drug or could be earlier. Organ involvement is very rare. ANCA-associated vasculitis is relatively a common cause of glomerulonephritis (19%) in the very elderly aged 80 years and over and rises to 33% in patients presenting with acute kidney injury [27].

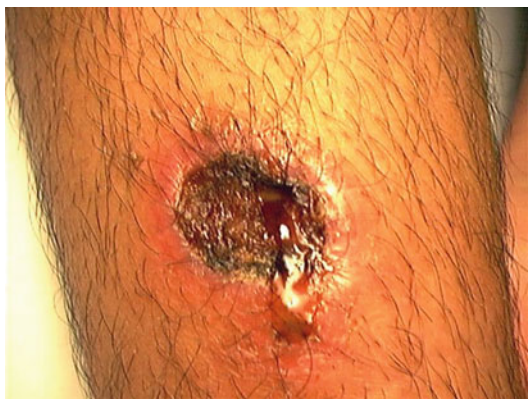


Fig. 1 Vasculitic ulcer (Reproduced, with kind permission, from Professor Nicholas Manolios)

Box 2 Secondary Vasculitis Drugs-Related

Penicillin
Cephalosporin
Sulphonamide
Thiazides
Phenytoin
Allopurinol
Propylthiouracil
Hydralazine

Information source: Vasculitis Foundation [25] and Suresh et al. [16]

Malignancy may trigger vasculitis [28]. Haematological malignancies and the lympo- and myeloproliferative diseases have been associated with small vessel vasculitis [29, 30]. Histology reveals necrotizing leukocytoclastic vasculitis with disruption of the endothelial integrity and neutrophil infiltration. Immunofluorescence staining for IgG, IgA, IgM, C3 and C4 is negative [29, 30]. In patients with ANCA-associated vasculitis, there is no difference between patients with and without malignancy. In patients with ANCA-associated vasculitis, malignancy should be considered in the differential diagnosis [31]. ANCA-associated vasculitis is relatively a common cause of glomerulonephritis (19%) in the very elderly aged 80 years and over and rises to 33% in patients presenting with acute kidney injury [27]. In the elderly, it has poor prognosis and rapid progression [5]. PR3-ANCA- and MPO-ANCA-positive vasculitis often occur in the elderly patient and cause deterioration of renal function [5].

Any part of the body can be affected [32, 33]. Vasculitis can present with signs and symptoms of systemic inflammation which may be

non-specific such as fever, fatigue, night sweats, weight loss and arthralgias [16] or present as pyrexia of unknown origin. The skin lesions may take the form of palpable purpura, urticaria, erythema multiforme, necrotic papules, ulcers and haemorrhagic papules. Respiratory involvement is suggested by cough, haemoptysis, breathlessness and nasal obstruction. Vasculitis commonly involves the kidney and can lead to end-stage renal disease. Acute or chronic renal failure and proteinuria suggest renal involvement and arthritis, arthralgia or myalgia musculoskeletal involvement. Symptoms relating to the eye are retinal vasculitis and uveitis.

Subclinical Entities

Giant cell arteritis (GCA) is vasculitis which involves the medium- and large-sized arteries of the extracranial branches of the carotid artery. The aortic arch can be involved. It is a panarteritis which predominantly infiltrated with lymphocytes, histiocytes and multinucleated giant cells bordering the internal elastic lamina followed by proliferation of the intima and reduction or occlusion of the lumen (Fig. 2). There is immune-mediated damage to the vessel wall. The immune response is initiated by dendritic cells and regulated by CD4-T cells which differentiate into vasculitic T cells [34, 35]. The Notch ligand pathway has a vital role in the initiation and maintenance of large vessel vasculitis, and inhibition of Notch signalling results in curbing cellular responses and diminishes CD4-T cell activation markers and T-cell proliferation [35]. The inflammatory process is patchy. It affects persons over the age of 50 years [36–38] with a mean age of 70 years. The onset may be gradual or abrupt. At the beginning, the symptoms may be non-specific [36] – constitutional symptoms such as malaise, weight loss, fever with the classic symptoms of jaw claudication, headache, scalp tenderness and visual impairment [36, 37, 39]. It is a chronic illness and may last for years. The temporal artery may be tender or pulseless or both in about half the number of patients. In about 40–60% of the patients, it is associated with PMR [40] which is characterized by pain in both shoulders and hips together with stiffness [36, 37, 39]. The thoracic and abdominal aorta can be involved infrequently leading to aortic dilatation or aneurysm. The erythrocyte sedimentation rate is usually markedly elevated but rarely it may be normal [38]. Often there is mild anaemia, and the serum alkaline phosphatase may be elevated. In a few patients with GCA, the temporal artery biopsy may not show changes for CGA as it does not affect every part of the artery. In which case, biopsy on the other side will be fruitful.

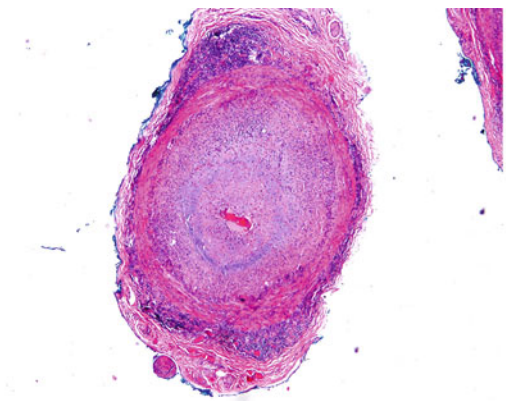


Fig. 2 (Low power) Histology of giant cell arteritis. There is mixed inflammatory cell infiltrate in the media, disruption of the internal elastic lamina and proliferation of the intima with reduction of the lumen (Reproduced, with kind permission, from Professor Nicholas Manolios)

EGPA (Churg-Strauss syndrome) is a rare form of vasculitis and is characterized by necrotizing vasculitis with eosinophilia [41]. There is a history of asthma or atopy. The lungs are nearly always involved with eosinophilic infiltrate. MPA (microscopic polyangiitis) bears a semblance to polyarteritis nodosa, Churg-Strauss syndrome microscopic polyarteritis nodosa and demonstrate the features of vasculitic syndromes such as hypersensitivity vasculitis. Renal involvement is common and pulmonary haemorrhage can occur [41]. GPA (Wegener's granulomatosis) is characterized by vasculitis, necrosis and granuloma formation. It affects both sexes equally at any age with a mean age around 40 years. The clinical features of some vasculitic disorders are shown in Table 1.

Table 1 Clinical features in some vasculitic disorders in the elderly

Disorder	Signs and symptoms
Large-sized vessel	
Temporal arteritis	Years headache, visual changes or loss of vision, jaw claudication, scalp tenderness, polymyalgia rheumatica
Medium-sized vessel	
Polyarteritis nodosa	Years multisystemic inflammatory nature, fever, malaise, skin ulcers, mononeuritis multiplex, peripheral neuropathy, intestinal ischaemia
Isolated CNS vasculitis	Headache, stroke, confusion
Small-sized vessel	
Churg-Strauss vasculitis	Adult onset asthma, eosinophilia, rhinitis
	Pulmonary infiltrates
Wegener's granulomatosis	Related to upper and lower respiratory
	Tract symptoms and kidney and ocular involvement
Microscopic polyangiitis	ANCA associated, kidneys
	Skin, lung, symptoms
Cryoglobulinemic vasculitis	Symptoms related to skin and glomeruli, arthritis, Raynaud's phenomenon
Drug-related vasculitis	Skin manifestations
	Symptoms related to lympo-myeloproliferative disorders
Infection-related vasculitis	Symptoms related to hepatitis B and C, HIV, *Campylobacter*, *Streptococcus*, *Staphylococcus*, EBV, among others

Information sources: Mansi et al. [8], Suresh [16], UNC Health [32] and emedicine health [33]

Diagnosis and Evaluation of Vasculitis in the Elderly

To arrive at a diagnosis, knowledge of the specific features of these diseases is required. The clinical features can be used to discern the size of the vessel affected and the specific type of vasculitis based on the above-mentioned and the pattern of the clinical features [42]. A structured approach based on disease staging is the key to efficient management [43]. An assessment system is necessary to systematize a treatment plan as well as to document progress and relapse [44]. The use of the Birmingham Vasculitis Activity Score is recommended in clinical practice [5].

Multisystem involvement with combination of symptoms together with symptoms of a systemic illness should alert the clinician of the possibility of vasculitis. Routine laboratory tests include a full blood count, erythrocyte sedimentation rate, C-reactive protein and liver and renal function tests. The results may be non-specific. Secondary forms of vasculitis have to be distinguished from primary as infections, and other underlying secondary vasculitis may require a different approach [45]. Blood cultures should be done to exclude an infection. Evaluation should include a tissue diagnosis if possible. Vasculitis is often focal or segmental, and biopsies may not show inflammation even if the entire vessel is affected; hence, sampling from multiple areas or long segments of a vessel may increase yield. Having confirmed the diagnosis, it will be necessary to determine the aetiology.

Laboratory evaluation will involve rheumatoid factor, antinuclear antibody, hepatitis profile, cryoglobulin and antineutrophilic cytoplasmic antibodies (ANCA), complement levels, eosinophil counts and IgE level and biopsy [16]. Now in use is the solid-phase ELISA to detect antibodies specific for the major autoantigen proteinase-3 (PR3ANCA) which correlates with the cANCA staining pattern or myeloperoxidase (MPOANCA) which correlates with the pANCA staining pattern. The detection of ANCA will support the diagnosis

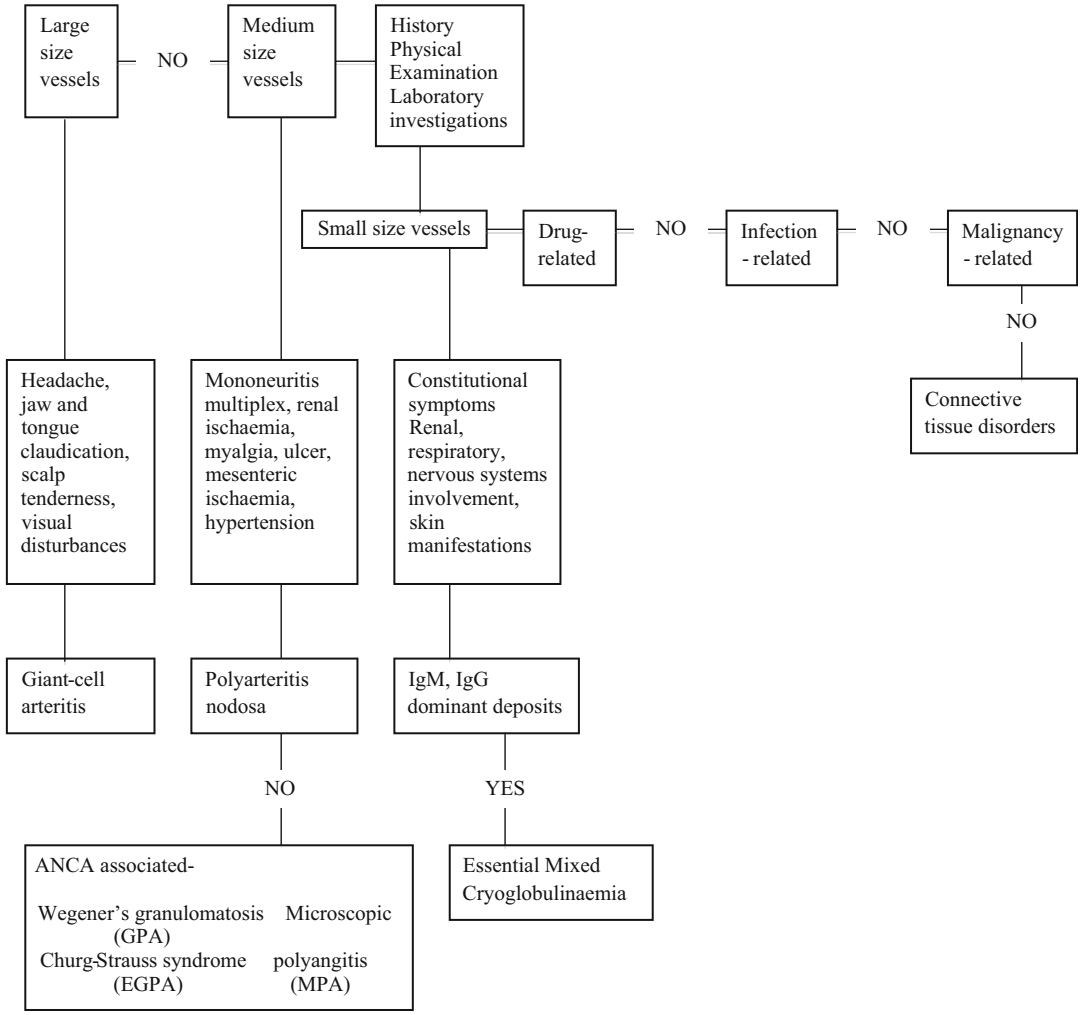


Fig. 3 Evaluation of vasculitis

of small vessel vasculitis such as Churg-Strauss syndrome, Wegener's granulomatosis or microscopic polyangiitis and certain types of drug-induced vasculitis [46]. The presence ANCA directed against proteinase 3 or myeloperoxidase is strongly suggestive of the pauci-immune small vessel vasculitis [47]. In Wegener's granulomatosis, the ANCA is directed against proteinase 3 (PR3), whereas in microscopic polyangiitis, it is directed against myeloperoxidase [47]. Serum complement levels (C3, C4, CH50) and evaluation for circulating immune complexes may be useful in some patients. Immune complex-mediated vasculitis is indicated by the presence of hypocomplementemia. X-ray of the chest and of sinuses and neuroimaging (CT scan and MRI) and an angiogram were indicated. Figure 3 suggests an algorithm for evaluation of vasculitis.

Treatment

During the past few years, there have been significant advances in the clinical management of vasculitis. The primary care physician is nearly always the first point of contact for a patient seeking medical attention. A careful history and physical examination may be able to detect signs of target organ involvement suggestive of vasculitis. The treatment will be very much determined by a careful evaluation, the cause, the extent and

Table 2 Treatment of major systemic vasculitis

Disease	Corticosteroids	Cyclophosphamide	Other[a]
Giant cell arteritis	+++[b]	–	–
Polyarteritis nodosa	+++[b]	++	+
Wegener's granulomatosis	+++[b]	++	Methotrexate
Churg-Strauss syndrome	+++[b]	++	+
Microscopic polyangiitis	+++[b]	++	+
Cryoglobulinaemia plasmapheresis	++	–	Antiviral therapy if with Hepatitis C
Hypersensitivity vasculitis	++ to +++	–	NSAIDS
	Moderate to severe cases		

Information Source: Roane and Griger [42]
[a]High doses
[b]Include azathioprine, cyclosporine, plasma exchange, intravenous immunoglobulin and monoclonal antibodies

the severity of the disease [48]. In the case of secondary vasculitis, removing the cause may suffice. The treatment of primary vasculitis has three aspects, namely, (i) induction of remission, (ii) maintenance of remission and (iii) treatment of relapse [8] (Table 2).

i. Induction of remission

Severe and rapidly progressive: Therapeutic strategies include the use of corticosteroids in conjunction with either conventional or biologic agents for induction or maintenance of remissions [49]. High-dose corticosteroids and cyclophosphamide [50] with additional therapy are used in life-threatening cases [41]. Methylprednisolone IV and oral prednisone are used concurrently. Cyclophosphamide is used orally but if the patient is unable to tolerate it, oral cyclophosphamide IV may be used. Induction of remission may take 3–6 months. In ANCA-associated vasculitis, pulsed cyclophosphamide had shown success [51] but several studies have raised the question of its efficacy [50]. It is less toxic than continuous oral cyclophosphamide but has a higher relapse rate [51]. Current strategies have focussed on minimizing cyclophosphamide or eliminating its use, and randomized trials have shown that rituximab is not inferior to cyclophosphamide for induction of remission with severe GPA or MPA [52]. Methylprednisolone therapy with 0.5–.0 g of methylprednisolone for 3 days can be used in initial treatment of severe ANCA-associated vasculitis to control acute symptoms [5]. Additional plasmapheresis is effective in severe ANCA-associated vasculitis [44] in patients with pulmonary haemorrhage and renal failure who need haemodialysis [5].

ii. Maintenance of remission

Prednisone dose is tapered down together with cyclophosphamide maintenance for 12–18 months. The lowest dose of prednisone should be used. During treatment blood counts and liver function tests should be done periodically and monitored closely for possible side effects of steroids. The treatment is continued till disease activity is minimal [53]. Azathioprine or methotrexate can replace cyclophosphamide for maintenance therapy once remission is achieved [54]. Azathioprine has been shown to be as effective as continued cyclophosphamide in maintaining remission [55]. Infection prevention is requisite because of the high morbidity in the elderly. The commonly used drug in the prevention is trimethoprim 0.5–1 mg daily [5].

iii. Relapse

Patients must be closely followed for signs and symptoms of relapse. Those who have frequent relapses may need to take immunosuppressants indefinitely. For the mild and less severe forms, lower doses of steroids and less potent immunosuppressants such as

methotrexate (with folate) and azathioprine are used. These drugs have also been used to maintain remission. Plasma exchange is indicated as an adjuvant therapy in patients with renal involvement [54].

Management of Giant Cell Arteritis (GCA)in Older Patients

Oral prednisolone 40–60 mg/day is commonly used initially in GCA, and corticosteroids [36] are gradually reduced guided by the erythrocyte sedimentation rate and/or C-reactive protein [38]. Duration of therapy can be up to 5 years or more for complete clinical remission to occur [36], and the rate of reduction will depend on the patients' response, considering the risks of and in particular high-dose and long-term use [56]. In patients with frequent relapses and/or corticosteroid toxicity, methotrexate may be useful [38]. The use of low-dose aspirin should be considered in reducing ischaemic complications [38, 56]. The use of vitamin D, bisphosphonates, and oral calcium supplementation is appropriate for the side effects associated with long-term use of glucocorticosteroids [37].

Impact

In the very elderly, vasculitic syndromes have a bad prognosis, majority deteriorating suddenly leading to death or severe functional impairment [4]. Patients over the age of 75 years or older with ANCA-associated vasculitis have a higher mortality related to renal involvement, and they have a greater risk of dying in the first 6 months of diagnosis [7]. In another study of patients with ANCA-associated vasculitis on immunosuppressive therapy, 57% were osteopenic and 21% were osteoporotic [57]. Independent of renal involvement, advanced age is a risk factor for mortality in ANCA-related vasculitis [7, 58]. Pulmonary involvement is more severe in patients age 65 years and over with ANCA-related vasculitis, and the prevalence of interstitial fibrosis is higher in this age group [59].

The true socio-economic impact of the vasculitis is not entirely known [60]. In the United States, a rough estimate of the expenditure for vasculitis-related hospitalization amounted to $150 million per year [60]. In a study of 12 patients, with an average age of 82 years with primary and secondary vasculitis, 83% of them deteriorated rapidly from infections, malnutrition or functional impairment or died abruptly [6]. Disease in the elderly poses special problems and is prone to steroid-related adverse effects. In the study, the impact on the elderly was noted in which 53% of 43 patients with giant cell arteritis developed major steroid complications [61, 62], and the adverse effects included cardiovascular, gastrointestinal and ocular infection and diabetes (Boxes 3 and 4).

Box 3 Key Points: Vasculitides

The second International Chapel Hill Consensus Conference (CHCC) held in 2012 revised the nomenclature [10], and the terms for Wegener's granulomatosis, Churg-Strauss syndrome and Henoch-Schonlein purpura were changed to granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and IgA vasculitis for Wegener's granulomatosis, Churg-Strauss syndrome and Henoch-Schonlein purpura, respectively.

The detection of antineutrophil cytoplasm autoantibodies (ANCA) has made it possible for small vessel vasculitis to be further classified as ANCA-associated and non-ANCA-associated vasculitis [8].

There are several mechanisms involved in the vascular inflammation, namely, immune complex disease [15], antibody-mediated disease, [15] antibody-dependent cellular cytotoxicity and endothelial activation, among others.

In primary vasculitis, there is no known cause. Secondary vasculitis occurs when the vascular system is injured by infection, drug or toxin.

(*continued*)

Box 3 Key Points: Vasculitides (continued)

Major symptoms are from skin rash, joint pains and lymphadenopathy.

Evaluation should include a tissue diagnosis if possible. An assessment system is necessary to systematize a treatment plan as well as to document progress and relapse [44].

The use of the Birmingham Vasculitis Activity Score is recommended in clinical practice [5].

Therapeutic strategies include the use of corticosteroids in conjunction with either conventional or biologic agents for induction or maintenance of remissions [49].

In the very elderly, vasculitic syndromes have a bad prognosis, the majority deteriorating suddenly leading to death or severe functional impairment [4].

Box 4 Key Points: Vasculitis

The detection of antineutrophil cytoplasmic autoantibodies (ANCA) has made it possible for small vessel vasculitis to be further classified as ANCA-associated and non-ANCA associated vasculitis [8].

The ANCA-associated vasculitides are a group of disorders which include Wegener's granulomatosis (GPA), microscopic polyangiitis (MPA) and Churg-Strauss syndrome EGPA).

Infection-related vasculitis constitutes the most common cause of secondary vasculitis.

Vascular damage can be caused directly or indirectly by a variety of organisms, be it viral, bacterial and fungal infections. Hepatitis B and C, HIV [18–20], EBV and organisms such as *Streptococcus*, *Staphylococcus* and *Campylobacter* can cause vasculitic syndromes.

An assessment system is necessary to systematize a treatment plan as well as to document progress and relapse [44].

Box 4 Key Points: Vasculitis (continued)

The use of the Birmingham Vasculitis Activity Score is recommended in clinical practice [5].

The treatment of primary vasculitis has three aspects, namely, (i) induction of remission, (ii) maintenance of remission and (iii) treatment of relapse [8].

In the very elderly, vasculitic syndromes have a bad prognosis, the majority deteriorating suddenly leading to death or severe functional impairment [4].

Multiple Choice Questions

1. Each of the following about Wegener's granulomatosis (WG) is true, except:
   A. It increases with advancing and peaking in middle aged and elderly and is common in white people of European origin.
   B. It affects the lungs, kidneys and other organs.
   C. It involves medium- and large-sized vessels.
   D. Antineutrophil cytoplasmic antibody (ANCA) is responsible for WG.
2. Each of the following is true of polyarteritis nodosa (PAN), except:
   A. The characteristic active lesion is necrotizing vasculitis with fibrinoid necrosis.
   B. It has been reported in association with hepatitis B in approximately 15–30% of cases.
   C. The most common signs and symptoms of PAN are related to its multisystemic inflammatory nature.
   D. ANCA has been reported in in the majority of cases with PAN.
3. The following in relation to vasculitis is true, except:
   A. Hypersensitivity vasculitis presents most commonly as palpable purpura.
   B. Henoch-Schonlein purpura is characterized by palpable purpura with varying degrees of glomerular nephritis and gastrointestinal involvement.

C. Granulomatous inflammation together with giant cell formation is a characteristic of temporal arteritis.
D. Takayasu arteritis is common in white people of European origin.

4. Each of the following statements relating to the different vasculitis is true, except:
A. Antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitides (AASV) is made up of Wegener's granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome.
B. In Churg-Strauss syndrome, the lungs are nearly always involved.
C. Microscopic polyangiitis generally demonstrates segmental necrotizing glomerulonephritis.
D. In Wegener's granulomatosis, the ANCA is directed against myeloperoxidase, whereas in microscopic polyangiitis, it is directed against proteinase 3 (PR3).

MCQ Answers

1 = C; 2 = D; 3 = D; 4 = D

A Case Study of a Patient with Severe Infection-Induced Vasculitis[a]

Presentation: A 51-year-old meat handler presented with diarrhoea and rash on his leg. He was not on any medication. He had had two similar episodes a few years earlier. Examination revealed a thickened tender long saphenous vein and a warm tender urticarial violaceous rash on his right leg. The right Achilles tendon was thickened and tender, and a few days later, he developed an extremely painful heel.

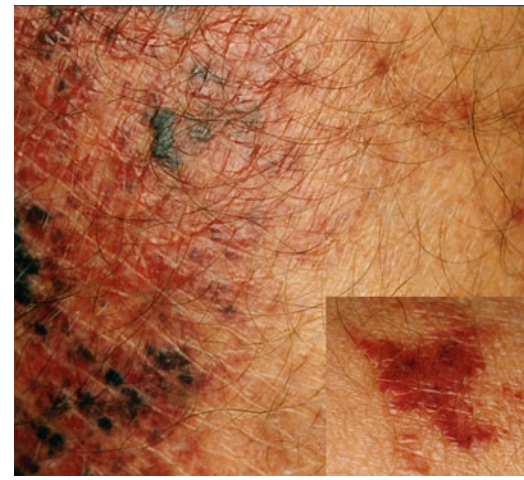
The WBC was 9 × 106/L (neutrophils71%; band forms 16%), platelet count 170 × 106/L and ESR 54 mm/1/h. Activated partial thromboplastin test (APTT) was 54 s and a week later 41 s. ANA, monoclonal antibodies, cryoglobulins and anti-cardiolipin antibodies were not detected. Complements and RA factors were normal; stools culture gave *Campylobacter jejuni* although the blood culture was negative. The Doppler revealed old thrombus in the distal popliteal vein.

Skin biopsy showed extravascular red blood cells, oedema and endothelial swelling of the capillaries per vascular infiltration. Immunofluorescence revealed granular deposits of IgM (traces) and C3 (1+) in occasional vessels of the superficial venous plexus, granular deposits of C3 in the dermo-epidermal junction and extensive deposits of fibrinogen (3+) in and around the vessels. These findings were consistent with immune complex vasculitis.

Comment

Worldwide the *Campylobacter* species are one of the major causes of bacteria-related diarrhoea [63]. There is considerable circumstantial evidence to support the implication of *Campylobacter jejuni.* The immune vasculitis, the thrombotic vascular events, the reactive arthritis and the haematological abnormalities are supporting evidence of *C. jejuni* involvement. Bacteria can cause damage to the vessel walls directly as toxins or by their products acting as antigens immune complex reactions.

[a]Reproduced from Nagaratnam et al. [64].



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Part XIV

Connective Tissue Disorders in the Elderly

Connective tissue disorders form a wide spectrum of disorders including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjorgren's syndrome (Ss-S), giant cell arteritis, polymyalgias rheumatica, polyarteritis nodosa, and overlap syndromes – mixed connective tissue disease (MCTD) and inflammatory muscle disease (dermatomyositis/polymyositis). Part XIV provides an overview of the prevalence and mechanisms and focuses on the age at onset of these disorders. Systemic lupus erythematosus can affect individuals of every age. The usual age is between 15 and 40 years but can present in the sixth decade and older, and the clinical course and manifestations differ from that seen in persons whose disease onset is in the second–fourth decades. The pathogenesis of systemic sclerosis (SSc) is characterized by immune and endothelial activation, vascular dysfunction, and overproduction of extracellular matrix. The late onset is clinically and immunologically different from the early onset. In the elderly, Sjogren's syndrome should be considered when sicca symptoms occur with systemic manifestations. The overlap syndromes are characterized by a combination of major features of one or more rheumatic diseases and mixed connective tissue diseases (MCTD) which is a special form of overlap syndrome. Both age and SLE are well-recognized risk factors for coronary artery disease. Late-onset SSc is associated with malignancy, severe Raynaud's phenomenon, cardiac and pulmonary complications, and poor functional status. Poor prognosis in Sjogren's syndrome is associated with older age, delayed or inadequate treatment, and malignancy.

Systemic Lupus Erythematosus

62

Contents

Abstract

Systemic lupus erythematosus can affect individuals of every age. The usual age is between 15 and 40 years but can present in the sixth decade and older, and the clinical course and manifestations differ from that seen in persons whose disease onset is in the second–fourth decades. SLE is an autoimmune disorder characterised by multisystem involvement. Autoimmunity in systemic lupus erythematosus (SLE) is brought about in all probability by a disorder, primary to the T cell, and is expressed as an abnormal immunological response to self-antigen. In the elderly with SLE, the female/male ratio is 2:1, and 10–20% of the cases occur in the elderly. The common manifestations in the elderly at onset are non-specific and include myalgia, weakness, fatigue, fever weight loss and arthralgia. The late onset displays a distinct antibody profile. Anti-DNA antibodies, anti-RNP antibodies and anti-Smith antibodies occur less frequently.

Keywords

Systemic lupus erythematosus · Autoimmunity · Late-onset SLE · Immunosuppressive agents

Introduction

Connective tissues such as the tendon, skin, bone and cartilage which perform varied mechanical functions [1] are made of components such as collagen, proteoglycan, elastin or glycoprotein [2]. Each component has specific function, for example, tensile strength depends on the collagen component and resistance to compression to proteoglycan [3]. During the ageing phase, changes

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_63

in the properties of the collagen and elastin are associated with intranuclear cross-linking and side chain modification [2]. The cross-linking involves two mechanisms, one an enzymic process and, the other, a non-enzymic adventitious reaction with glucose, resulting in tissue dysfunction in the elderly [2].

Connective tissue disorders form a wide spectrum of disorders including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjogren's syndrome (Ss-S), giant cell arteritis, polymyalgia rheumatica, polyarteritis nodosa, overlap syndromes – mixed connective tissue disease (MCTD) – and inflammatory muscle disease (dermatomyositis/polymyositis) [4, 5]. All are immune complex-mediated autoimmune conditions. SLE is an autoimmune disorder characterised by multisystem involvement [6, 7]. The pathological process involves the skin, blood vessels, vessels in the glomerulus, gastrointestinal tract, lungs, brain and cardiovascular system [8]. There is evidence to show that immunosenescence directly affects gene expression culminating in T-cell immunodysfunction [9]. Autoimmunity in systemic lupus erythematosus (SLE) is brought about in all probability by a disorder, primary to the T cell, and is expressed as an abnormal immunological response to self-antigen [4].

Clinical Manifestations

Systemic lupus erythematosus can affect individuals of every age [10]. The usual age is between 15 and 40 years [4] and can present in the sixth decade and older, and the clinical course differs from that seen in persons whose disease onset is in the second–fourth decades [9]. In the young onset the female/male ratio is 6–10:1 [4]. In the elderly with SLE, the female/male ratio is 2:1, and 10–20% of the cases occur in the elderly [6, 11, 12]. The diagnosis is often delayed in the late onset [13, 14]. The onset and course of the disease are largely influenced by several multiple genes and environmental factors over time [10]. The clinical spectrum of SLE ranges from mild systemic illness, arthritis, malar rash, photosensitivity and at the other end a fulminating illness with multi-organ involvement. The late-onset SLE is clinically and immunologically different than the adult onset. The common manifestations in the elderly at onset are non-specific and include myalgia, weakness, fatigue, fever weight loss and arthralgia [7, 15]. Malar rash, other cutaneous manifestations, arthritis, nephritis and neurological involvement are less frequent. Alopecia is seen in 24% of elderly patients compared to 44.9% in younger patients [16] (Fig. 1). On the contrary, serositis, pulmonary involvement (interstitial lung disease) and Sjogren's syndrome are frequently found. It has a more benign course with less major organ system involvement than that of the young onset. Despite the benign course, the late-onset patients may not have a good prognosis in terms of survival. The clinical features of late-onset lupus are very similar to drug-induced lupus (DIL), and in general fevers, arthralgias and serositis are more common in DIL [17].

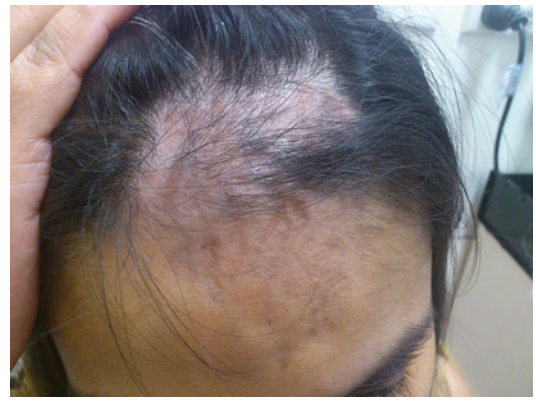

Fig. 1 Elderly female with alopecia due to SLE (Reproduced, with kind permission, from Professor Nicholas Manolios)

Diagnosis

The late onset displays a distinct antibody profile. Anti-DNA antibodies, anti-RNP antibodies and anti-Smith antibodies occur less frequently [16, 18]. Contrary to rheumatoid factor, anti-La

antibodies are more often positive and occur more frequently, and this may have a relationship to the high frequency of Sjogren's syndrome. Furthermore the late onset has hypocomplementaemia. Table 1 summarises the differences and similarities between late-onset and early-onset lupus.

Treatment

There is no cure for SLE, and the aim of treatment is to slow progression and prevent organ damage, and hence an early diagnosis is necessary. Treatment will depend on the severity, clinical manifestations and age of onset. Older people can often be managed conservatively. According to the European League Against Rheumatism (EULAR) guidelines for the treatment of SLE, patients without major organ manifestations are benefited with glucocorticoids or antimalarial agents [19]. Acetaminophen or nonsteroidal anti-inflammatory drugs (NSAID) may be used in patients who are at low risk for complications with these drugs [20]. There are two types of cyclooxygenase (COX) designated as COX-1 and COX-2. The most commonly available NSAIDs (e.g. naproxen) are non-selective inhibitors of both COX-1and COX-2. Selective COX-2 inhibitors (e.g. rofecoxib, celecoxib) are equally efficacious but do have lower incidence of gastrointestinal side effects. The commonly used antimalarial is hydroxychloroquine. In refractory cases or when steroid doses cannot be reduced in the long term, immunosuppressive agents such as azathioprine, belimumab, methotrexate or mycophenolate mofetil may be considered [24]. If there is a history of venous or arterial thrombosis or antiphospholipid antibody syndrome, an anticoagulant will be necessary.

Impact

Both age and SLE are well-recognised risk factors for coronary artery disease [14]. Malignancy, hypertension and disease duration have a negative

Table 1 Distinguishing features between late-onset and early-onset SLE

	Elderly (late) onset	Adult (early) onset
Age of onset (years)	>50	<50
Gender	F>M 2–4:1	F.M 6–10:1
Mode of onset	Insidious	Acute
Clinical expression		
Cutaneous		
Malar rash	Less frequent	Frequent
Photosensitivity	Less frequent	Frequent
Purpura/vasculitis	Less frequent	Frequent
Alopecia	Less frequent	Frequent
Raynaud's phenomenon	Less frequent	Frequent
Organ system involvement	Less major	More major
Serositis	Frequent	Less frequent
Pulmonary involvement	Frequent	Less common
Renal disease		
Nephrotic syndrome	Less frequent	Frequent
Nephritis	Less frequent	Frequent
Neurological/ neuropsychiatric	Less frequent	Frequent
Sjogren's syndrome	Frequent	Less frequent
Cardiomyopathy and hypertension	More frequent	Less frequent
Neoplasms	More frequent	Less frequent
Laboratory profile		
Anti-nuclear antibodies	Mostly positive	Mostly positive
Anti-dsDNA antibodies	Lower prevalent	More prevalent
Hypocomplementaemia	Lower prevalent	More prevalent
Rheumatoid factor	More positive	More positive
Anti-Ro/Sjogren's antibodies	More often positive	Less often positive
Anti-La/SSB	More often positive	Less often positive
Anti-U1RNP	Less common	More common
Anti-Smith antibodies	Less common	More common
Disease severity	Benign	Severe
Long-term survival	Poor outcome	Better outcome

Information sources: Rovensky and Tuchynova [6]; Lazaro [11]; Font et al. [14]; Bertoli et al. [18]; Boddaert et al. [16]; Martinez-Burro et al. [21]; Alonso et al. [22]; Domenech et al. [23]

impact in the late onset with increase in mortality [21]. Patients with late onset show higher mortality than the younger patients [18]. The age of onset and the presence of comorbidities especially those resulting in accrual damage may in part be responsible for the mortality [9, 25] (Box 1).

Box 1 Key Points: Systemic Lupus Erythematosus (SLE)

- SLE is an autoimmune disorder with multisystem involvement [6, 7].
- About 10–20% of SLE can occur in the elderly for the first time [6, 11, 12].
- The late onset is clinically and immunologically different from the early onset.
- The late onset has a distinct antibody profile [16, 18].
- The late onset has a benign course, but the long-term survival is poor.

Multiple Choice Questions

1. The following are true in relation to the changes that occur in the connective tissues with ageing, except:
   A. During the ageing phase changes in the properties of the collagen and elastin are associated with intranuclear cross-linking and side chain modification.
   B. The immune activity of the innate immune system in later life is evidenced by the absence of elevated markers of inflammation.
   C. The susceptibility of the elderly to infectious diseases, autoimmunity and cancer is directly or indirectly related to age-related changes of the immune system.
   D. Connective tissue disorders are all immune complex-mediated autoimmune conditions.
2. The following are true with regard to late-onset systemic lupus erythematosus (SLE), except:
   A. The late-onset SLE is clinically and immunologically different than adult onset.
   B. Malar rash, arthritis, nephritis and neurological involvement are less frequent.
   C. The late onset does not have a good prognosis in terms of survival.
   D. Anti-DNA antibodies and anti-RNP antibodies are frequent.

MCQ Answers

1 = B; 2 = D

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Systemic Sclerosis (SSc)

63

Contents

Abstract

Epidemiological studies have underscored the incidence of SSc in the sixth, seventh and eighth decades of life. The pathogenesis of systemic sclerosis (SSc) is characterised by immune and endothelial activation, vascular dysfunction and overproduction of extracellular matrix. The late onset is clinically and immunologically different from the early onset. There are two subsets of SSc, diffuse cutaneous SSc (dcSSc) which is associated with progressive fibrosis of skin and internal organs and the other limited cutaneous.

Keywords

Systemic sclerosis · Late onset · Early onset · Diffuse cutaneous · Diffuse cutaneous · CREST syndrome

Introduction

There is evidence to suggest that the incidence of progressive SSc in the elderly is more common than in younger age group [1]. Most patients with SSc present in the third or fourth decade of life [2]. The incidence in patients over 75 years with systemic sclerosis is around 20 per million per year, and the peak incidence in white females is between 65 and 75 years and in white males over 75 years [3]. Epidemiological studies have underscored the incidence of SSc in the sixth, seventh and eighth decades of life [3–5]. Vascular dysfunction, overproduction of the cellular matrix and immune and endothelial activation constitute the pathogenesis of SSc [6, 7].

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_62

Clinical Manifestations

Age of onset is commonly between the ages of 40 and 50 years [8]. There is however another subgroup with onset later in life. Some investigators have considered late onset as greater than 65 years [9] but others at or beyond 75 years [10]. There are two subsets of SSc, diffuse cutaneous (dcSSc) which is associated with progressive fibrosis of skin and internal organs [10] and the other limited cutaneous [10]. CREST syndrome is considered as limited cutaneous [11] and is characterised by calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly and telangiectasia (Fig. 1). They have different disease courses and prognosis [2]. The skin becomes hidebound; the nose is pinched; the lips are thinned out resembling a fish mouth, telangiectasia (Fig. 2) and calcinosis (Fig. 3).

There is deformity of the terminal phalanges with contractures of the digital joints, sclerodactyly and hypo- and hyperpigmented skin (Fig. 4). A study of 123 patients with SSc 75 years and older showed that pulmonary hypertension occurred more frequently, and fewer patients had digital ulcers [10]. Older SSc patients are at greater risk for renal impairment, cardiac disease and muscle weakness [9]. Earlier reports indicated that late-onset SSc is a milder form of the disease with minimal skin and internal organ involvement and decreased mortality [1, 12], but subsequent data indicates that late-onset SSc is a more aggressive disease [13] and the risk of death increases for each year by 5% [14]. It is not always progressive and prognosis variable. Table 1 summarises the distinguishing features between late-onset and early-onset SSc.

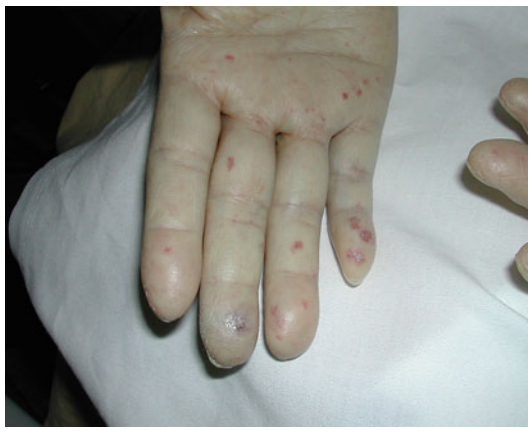

Fig. 1 Shows Raynaud's phenomenon, sclerodactyly and telangiectasia (Reproduced, with kind permission, from Professor Nicholas Manolios)

Diagnosis

Skin thickening with Raynaud's phenomenon with varying degrees of internal organ involvement provides the diagnosis of SSc. Raynaud's phenomenon may be the only early manifestation

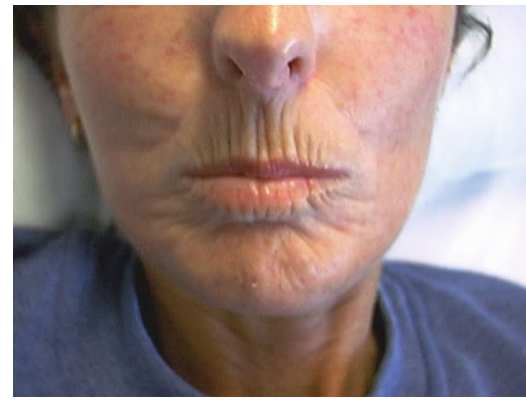

Fig. 2 Showing fish mouth, pinched nose and telangiectasia (Reproduced, with kind permission, from Professor Nicholas Manolios)

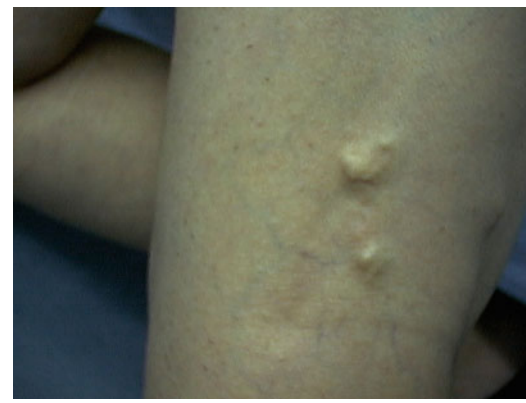

Fig. 3 Shows calcinosis cutis (Reproduced, with kind permission, from Professor Nicholas Manolios)

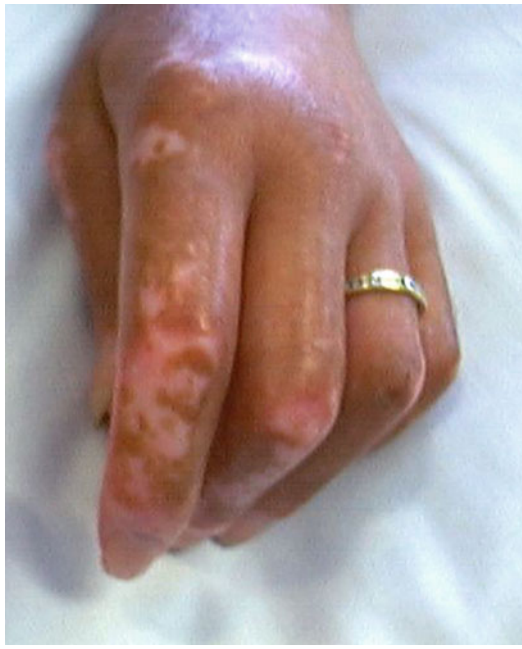

Fig. 4 Shows digital contracture of the digital joints, hidebound skin with hypo- and hyperpigmented areas (Reproduced, with kind permission, from Professor Nicholas Manolios)

of SSc. Nailfold capillary microscopy can help to determine primary Raynaud's disease from secondary Raynaud's (Raynaud's phenomenon) [18]. Most patients with dcSSc have one or more of the following autoantibodies positive, namely, auto-centromere antibodies (ACA), anti-RNA polymerase III and anti-topoisomerase I [18].

Treatment

Several therapies are available in the treatment of SSc, and the aim of treatment is to slow the progress of the disease, to improve vascular function and to provide supportive and symptomatic care [2]. The anti-inflammatory drugs, NSAIDs and corticosteroids, are useful in inflammatory states involving the joints, muscles, pericardium and pleura. They are of little use in inflammation of the skin and SSc-associated tissue injury [19]. Corticosteroids can increase the risk of renal crisis, and ACE inhibitors are known to reverse the vasospasm associated with SSc renal crisis [19]. The most effective vasodilators are the calcium channel blockers (e.g. nifedipine) and are the first-line agents to be used in Raynaud's phenomenon [20]. The immunosuppressive drugs include cyclophosphamide, mycophenolate mofetil, cyclosporine and methotrexate [19]. Cyclophosphamide is useful in patients with interstitial lung disease associated with scleroderma [21]. Aspirin in low dose has been recommended in Raynaud's phenomenon [2]. Bosentan, an endothelial receptor antagonist, has proved effective for the prevention of ischaemic digital ulcers [20, 22] and improved the blood flow to the lungs [20]. D-penicillamine has been used in patients with dcSSc in an effort to slow fibrosis [2]. Oral endothelial receptor antagonists, PDE5 inhibitors and parenteral prostanoids are included in the treatment of pulmonary hypertension [2].

Table 1 Distinguishing features between late-onset and early-onset systemic sclerosis (SSc)

Age of onset	<65 years	>65 years
Gender	Females	Females
Clinical expression		
Skin – diffuse	Present	Extensive
Digital ischaemia	Frequent	Less frequent
Renal	Frequent	More frequent
Muscle weakness	Frequent	More frequent
Pulmonary hypertension	Frequent	More frequent
Diastolic dysfunction		
and conduction deficits	Frequent	More frequent
Myositis	Frequent	Less frequent
Oesophageal involvement	Frequent	Less frequent
Raynaud's	Present	More severe
Relationship to		
Malignancy	Frequent	More frequent
Centromere antibodies (ACA)	Frequent	More frequent
Prognosis	Poor	Poorer

Information sources: Manno et al. [8]; Hugle et al. [10]; Manno et al. [9]; Derk et al. [15]; Czirjak et al. [16]; Albo et al. [17]

Impact

Late-onset SSc is associated with malignancy [15], severe Raynaud's phenomenon, cardiac and pulmonary complications and poor functional status [8]. The late-onset SSc is a poor prognostic indicator related to both severity and comorbidities [15]. Older patients have a greater risk of pulmonary hypertension, interstitial lung disease and renal impairment [8] and are common causes of death [22]. Other poor prognostic indicators are older age, male gender and involvement of internal organ system [2] (Box 1).

Box 1 Key Points: Systemic Sclerosis (SSc)

- The pathogenesis of systemic sclerosis (SSc) is characterised by immune and endothelial activation, vascular dysfunction and overproduction of extracellular matrix [6, 7].
- Age of onset is commonly between 40 and 50 years [8].
- There is another subgroup with onset later in life (late onset) [9, 10].
- There are two subsets of SSc, diffuse cutaneous associated with progressing fibrosis of the skin and internal organs and limited cutaneous [10].
- The late onset is clinically and immunologically different from the early onset.
- Renal, muscle weakness, pulmonary hypertension and relationship to malignancy are more frequent in the late onset (see Table 1).
- Digital ischaemia/ulcers, myositis and oesophageal involvement are less prevalent (see Table 1).

Multiple Choice Questions

1. The following are true of late-onset systemic sclerosis (SSc), except:
   A. SSc patients 75 years and older showed that pulmonary hypertension and digital ulcers occurred more frequently.
   B. There are two subsets of SSc, diffuse cutaneous and the other limited cutaneous.
   C. In the late onset, there is a higher prevalence of centromere antibodies.
   D. Raynaud's phenomenon is much more severe in the late onset.

MCQ Answers

1 = A

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Sjogren's Syndrome

64

Contents

Abstract

The syndrome may present alone (primary) or in association with an underlying connective tissue disorder (secondary). In elderly people Sjogren's syndrome (SS) is subclinical, relatively common and benign. In the elderly Sjogren's syndrome should be considered when sicca symptoms occur with systemic manifestations. Approximately 40% of xerostomia in the elderly is due to Sjorgren's syndrome and accounts up to 20% of Sjorgren's syndrome; arthralgias, Raynaud's phenomenon and purpura were common extraglandular manifestations. It is important to distinguish age-related gland pathology, drug-induced ocular and oral dryness from that due to SS.

Keywords

Sjogren's syndrome · Xerostomia · Raynaud's phenomenon · Purpura

Introduction

The prevalence of SS is about 3% in people above the age of 50 years, and the usual age of onset is at age 40–60 years [1]. It is common in middle-age women and the mean age is 52.7 years [2]. Its prevalence increases with age [3]. The syndrome may present alone (primary) or in association with an underlying connective tissue disorder (secondary) [4]. Approximately 40% of xerostomia in the elderly is due to

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_64

Sjorgren's syndrome, and the elderly account in up to 20% of Sjorgren's syndrome [5]. In a study of 336 consecutive primary SS patients, in 21 (6%) the disease onset was after the age of 65 years [6]. In elderly people SS is subclinical, relatively common and benign [7].

Clinical Profile

SS at presentation is characterised by sicca symptoms of dry eyes (xeropthalmia) and/or dry mouth (xerostomia) due to a lymphocytic infiltration of the lacrimal or salivary glands or both [3, 8]. About 40% of the xerostomia in the elderly is due to SS [5]. In patients with disease onset after the age of 65 years, dry mouth and dry eye were the commonest occurrence. Arthralgias, Raynaud's phenomenon and purpura were common extraglandular manifestations [6]. However, Bostios et al. [6] found no statistical differences in relation to gender, disease duration and ocular and oral symptoms between the elderly onset and the young/adult onset. In the elderly there is often a delay between clinical onset and diagnosis, and this has been attributed to shared features of SS and old age [9].

Diagnosis

In the elderly the diagnosis of SS should be considered when systemic manifestations are associated with sicca symptoms [3]. The revised version of the American European Consensus Group (AECG) classification for diagnosis required the following, namely, the signs and symptoms of oral and ocular dryness, a positive salivary gland biopsy or autoantibodies against SSA/Ro and SSB/La antigens [10]. There is often a delay in the diagnosis in the late onset for the sicca symptoms have been frequently attributed to ageing and or medications [5], and it is important to distinguish age-related gland pathology and drug-induced ocular and oral dryness from that due to SS [9].

Treatment

Oral symptoms: Oral hygiene, salivary stimulation (sugar free chewing gum) and prevention of oral infection (antimicrobial mouth rinses) [4] and systemic stimulation of salivary secretion. Ocular symptoms: Topical (topical tear replacement) and followed by increased tear production. Two muscarine agonists, pilocarpine and cevimerline, have been shown to be effective [4, 11, 12]. Oral cevimeline has been shown to relieve subjective eye symptoms [12]. Systemic symptoms: An anti-CD20 monoclonal antibody (rituximab) that depletes B lymphocytes is a new potential therapy showing promise for severe inflammatory manifestations [4, 13].

Impact

Complications such as dental caries, corneal ulcerations, chronic oral infections and sialadenitis are preventable with early diagnosis [14]. Basic daily functioning such as eating, speaking and sleeping may be affected by the dryness in the mouth thus affecting the quality of life [15]. In SS there is a 20- to 40-fold increase in the incidence of lymphoma [16]. In the elderly, polypharmacy and increased rates of adverse events to medications make treatment complicated in the elderly [17]. Poor prognosis is associated with older age, delayed or inadequate treatment and malignancy (Box 1).

Box 1 Key Points: Sjogren's Syndrome

- Sjogren's syndrome (SS) is an autoimmune disorder characterised by lymphocytic infiltration and destruction of the salivary and lacrimal glands [8].
- The syndrome may present alone (primary) or associated with another connective tissue disorder [4].
- The usual age of onset is between 40 and 50 years and the late onset >65 years [1].

(*continued*)

Box 1 Key Points: Sjogren's Syndrome
(continued)

- The presentation is characterised by sicca symptoms, dry eyes and dry mouth [1].
- In the elderly SS should be considered when sicca symptoms occur with systemic manifestations [3].
- In the late onset the sicca symptoms are often attributed to ageing or to medications and hence a delay in the diagnosis [5].

Multiple Choice Questions

1. The following are true with Sjogren's syndrome (SS), except:
   A. It is an autoimmune disorder characterised by lymphocytic infiltration and destruction of the salivary and lacrimal glands.
   B. The syndrome may present alone (primary) or associated with another connective tissue disorder (secondary).
   C. Primary SS in the elderly is often clinical, severe and relatively less common.
   D. In the elderly sicca symptoms are often attributed to ageing and/or medications.

MCQ Answers

1 = C

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Overlap Syndromes and Inflammatory Myopathies

65

Contents

Abstract

The overlap syndromes are characterised by a combination of major features of one or more rheumatic diseases, and mixed connective tissue disease (MCTD) is a special form of overlap syndrome. Inflammatory myopathies are idiopathic and acquired and are differentiated into several subsets, namely, dermatomyositis, the most common; polymyositis, least common; inclusion body myositis, most common above the age of 50; overlap myositis; cancer-associated myositis; and immune-mediated necrotizing myopathy.

Keywords

Overlap syndromes · Mixed connective tissue disease (MCTD) · Inflammatory myopathies · Dermatomyositis · Polymyositis

Introduction

The overlap syndromes are characterised by a combination of major features of one or more rheumatic diseases, and mixed connective tissue disease (MCTD) is a special form of overlap syndrome [1]. They occur at any age, and the female/male ratio is 3.3:1 [2]. The symptoms include non-specific systemic symptoms such as fever, lethargy together with signs of SLE, SS and others. ANA and anti-U1-RNP Ab are usually raised [3]. Anti-UA1-70Kd is present, and anti-dsDNA is usually negative [4]. MCTD may go to develop other CTD such as scleroderma, SLE or an overlap syndrome [2]. The most common cause of death is pulmonary hypertension.

Inflammatory myopathies are idiopathic and acquired and are differentiated into several subsets, namely, dermatomyositis, the most common;

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_65

Table 1 Differences and similarities between young onset (juvenile) and adult/elderly onset dermatomyositis

	Young (juvenile)	Adult/elderly
Onset(years)	5–10–15 years	>50–60 years
Mode of onset	Rapid	Slow
Muscle weakness	Present	Present
Skin rashes	Present (atypical)	Present
	(Occurring anywhere in the body)	
Amyopathic myositis	Rare	Common
Complications		
Malignancy	Rare	Frequent
Interstitial lung disease	Rare	Common
Calcinosis	More frequent	Less common
Major organ vasculopathy	More common	Common
Laboratory		
Creatinine kinase ALT, AST		
	Raised more frequently	
Myositis-specific antibody <60%		80%
EMG		Features of chronic disease
Morbidity and mortality		Disability mortality about 10%

Information sources: Marie et al. [13]

polymyositis, least common; inclusion body myositis, most common above the age of 50 [5]; overlap myositis; cancer-associated myositis; and immune-mediated necrotizing myopathy [6]. Dermatomyositis is an autoimmune disease, an uncommon idiopathic inflammatory myopathy and often diagnosed in the elderly but can occur in the very young (juvenile). Women are more affected than men [5]. Rash and proximal muscle weakness are both common to juvenile dermatomyositis (JDM) and adult-onset dermatomyositis (DM) [7]. Skin rashes – bluish purple patches occur mostly on sun-exposed areas, heliotrope discoloration of the eyelids and Gottron papules, purplish spots on the knuckles. The rash may also involve the rest of the face, upper chest and elbows. Other clinical features such as calcinosis, interstitial lung disease and malignancy vary in the frequency between juvenile and adult disease [7]. Calcinosis is a common manifestation in juvenile dermatomyositis and can lead to skin ulceration and joint contractures [8, 9]. JDM is not associated with malignancy and is a systemic vasculopathy [10]. There is a close association between adult DM and malignancy [7], and about 80% of the malignancies are adenocarcinomas [8, 11] particularly rectal adenocarcinoma [12]. Lung involvement includes bacterial pneumonia due to oesophageal impairment and ventilatory insufficiency from respiratory muscle weakness [13] (Table 1).

On the other hand, amyopathic myositis is more common in adults, and myositis-specific antibodies can now be identified in about 80% of adults and less than 60% in the young [7, 14]. Amyopathic dermatomyositis is characterised by the typical skin rash without muscle involvement, and a small portion of them transform to a myopathic state [15]. However, muscle metabolism is abnormal in amyopathic patients using sensitive measures of muscle function [15].

Treatment

Corticosteroids have been recognised as effectual in the treatment of dermatomyositis [6, 10, 16] and may slow down the rate of progression. Immunosuppressive drugs and biological agents [10] are used as additional treatment to improve response and to reduce the side effects of corticosteroids [6]. High-dose intravenous immunoglobulin is reserved for refractory cases or with contraindications to immunosuppressive drugs [6].

Impact

Old age, race and bulbar, pulmonary and cardiovascular involvement are poor prognostic factors in adult DM [16]. Disease-related death is largely due to associated cancer and pulmonary involvement [17]. In the long term, myositis has a profound effect on quality of life and perceived disability

[17]. In adult inflammatory myopathies, the mortality rate ranges from 5% to 37% and the commonest causes are malignancy [8, 13], cardiovascular disease [8] and pneumonia due to ventilator insufficiency and oesophageal impairment [8, 13] (Box 1).

Box 1 Key Points: Inflammatory Myopathies – Dermatomyositis (DM)

- Inflammatory myopathies are idiopathic, acquired and differentiated into several subsets [5].
- Rash and proximal muscle weakness are both common to juvenile dermatomyositis (JDM) and adult-onset dermatomyositis (DM) [7].
- There is a close association between adult DM and malignancy, and about 80% of the malignancies are adenocarcinomas [7, 8, 11].
- Lung involvement in DM includes bacterial pneumonia due to oesophageal impairment and ventilatory insufficiency from respiratory muscle weakness [13].
- Amyopathic myositis is more common in adults, and myositis-specific antibodies can now be identified in about 80% of adults [7, 14].
- Corticosteroids have been recognised as effectual in the treatment of dermatomyositis [6, 10, 16], and additional medications include immunosuppressive drugs and biological agents [10].

Multiple Choice Questions

1. The following are true of dermatomyositis (DM), except:
   A. Elderly patients with DM have a lower frequency of adenocarcinoma of rectum compared to younger patients.
   B. In elderly patients, electromyography has a feature suggestive of a chronic form of the disease.
   C. Quality of life and perceived disability are the major effects of myositis.
   D. Side effects are the major drawback of long-term corticosteroids.

MCQ Answers

1 = A

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Part XV

Organic Disorders of the Brain

In 2013, the American Psychiatric Association published its fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). What was classified as "Delirium, Dementia, Amnestic and other Cognitive Disorders" in DSM-IV is now called "Neurocognitive Disorders." DSM-5 has replaced the term "dementia" with "major neurocognitive disorder (NCD) or mild neurocognitive disorder" but accepts "dementia" as an agreeable alternative. However, if the physician prefers the dementias can still be referred to by their accustomed names, for example, Alzheimer's dementia, vascular dementia, or frontotemporal dementia and in fact DSM-5 has included "or dementia" in parentheses when referring to major NCD. This review will retain the traditional term "dementia." Part XV reviews a range of topics such as delirium, dementias, and mild cognitive impairment with an emphasis on the age at onset of the disease.

In DSM-5, the term "consciousness" is no longer used, but no major changes had been made to the core elements of DSM-5 criteria for delirium. Dementia occurs in several neurodegenerative disorders, and presently characterized by neuropathological criteria, most distinctly Alzheimer's disease (AD), frontotemporal dementia (FTD), Lewy body dementia (LBD), and hippocampal sclerosis (HAS). It is estimated that 2% and 10% of dementia begin before the age of 65, according to the World Alzheimer Report, and is referred to as early-onset dementia. Early-onset Lewy body spectrum disorders have been described although rarer than AD and FTD in patients younger than 65 years. AD, FTD, and vascular dementia are the three common causes of young-onset dementias. Furthermore, there are challenges of diagnosing dementia in the oldest old and the prevalence for dementia in those 85 years and over ranges from 18% to 38%. Hence a wider differential diagnosis is necessary for early-onset dementia compared to late-onset dementia. The review also provides an overview of the symptomatic dementias, behavioral and psychological symptoms, and their management.

Acute Delirium in the Elderly: Diagnosis and Management

66

Contents

Abstract

Delirium is a disorder in which high cognitive and integrative functions become defective, resulting in disturbance of global inattention and attention-directed disorders. In DSM-5 the term 'consciousness' is no longer used, but no major changes had been made to the core elements of DSM-5 criteria for delirium. The changes to DSM-5 include (1) disturbance in attention and orientation to the environment; (2) disturbance that develops in a short period of time; (3) a change in the cognitive domain such as in memory, language and orientation; and (4) disturbances 1 and 3 that should not occur in the context of a severely reduced level of arousal such as coma. Although this excludes coma, as being characterised as delirium, severe inattention can be deemed to occur where there is reduced arousal impairing cognitive testing. The pathophysiology of delirium is complex and the mechanisms poorly understood. Severe deleterious effects on brain function can result from systemic inflammatory signals in the elderly in the presence of neurodegenerative disease. It is recognised as an important cause of morbidity and mortality

Keywords

Delirium · Acute confusional state · S100B a putative marker of CNS injury · DSM-5

Introduction

Delirium is a disorder in which high cognitive and integrative functions become defective, resulting in disturbance of global inattention and attention-directed disorders [1]. Basically, it is a disorder of reduction and erratic shifting of attention [2]. A number of terms have been used such acute delirium, acute confusional state, acute brain syndrome, toxic psychosis, ICU syndrome and acute organic syndrome [3, 4] to indicate generalised brain dysfunction. Currently, the preferred term is

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_69

'delirium' which is a more rational approach in clinical practice and research [5]. According to Mesulam [2] confusional state combines two processes. The first is closely related to 'arousal' and the second is phasic and involves 'selective attention'. The American Psychiatric Association has revised the diagnostic criteria in its fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). In the previous editions of DSM, the requirements for the diagnosis were alterations in attention and or arousal, that is, alterations in the content of consciousness. In DSM-5 the term 'consciousness' is no longer used [5], but no major changes had been made to the core elements of DSM-5 criteria for delirium. The changes to DSM-5 include (1) disturbance in attention and orientation to the environment; (2) disturbance that develops in a short period of time, (3) a change in the cognitive domain such as in memory, language and orientation; and (4) disturbances 1 and 3 that should not occur in the context of a severely reduced level of arousal such as coma [5, 6]. Although this excludes coma, as being characterised as delirium, severe inattention can be deemed to occur where there is reduced arousal impairing cognitive testing [7].

The incidence of delirium among hospitalised patients was reported to be between 6% and 56% [8–11]. One study found 42% of the patients with delirium were between the ages of 70 and 75 years and 58% in 76 years and over with 67% being females [12]. Although it is associated with a high risk for post-operative complications, only 32–66% of the patients are diagnosed and treated effectively [13, 14], and in another study, 32% of the cases went unrecognised by physicians [13]. It carries a high mortality and morbidity and healthcare costs [10, 15]. The stay in hospital is longer and has a higher death rate. It is a frequent complication in hospitalised patients with medical and surgical illnesses [16], and approximately 50% develop delirium [17]. It is a common complication of medical illnesses. The mortality rates of delirium in general medical wards have varied from 10% to 45% and more recently from 10% to 65% [10, 18]. When the mortality rates of patients with delirium were compared with those with dementia, the death rates numbered 23% and 4%, respectively, and in another study, it was 13.5% and 3%, respectively [19].

The pathophysiology of delirium is complex and the mechanisms are poorly understood [20]. Elderly people are particularly vulnerable to delirium most likely due to age-related cerebral changes and in the neurotransmitter systems [21]. There are several observations upholding the hypothesis that multiple neurotransmitter abnormalities occur in delirium [22]. Physical stressful events giving rise to increased cortical secretion of cytokines may have a role, and some cytokines can influence the activity of the neurotransmitters and these mechanisms can interact [21, 23, 24]. In delirium, S100B, a putative marker of CNS injury, is associated with increased concentrations in the cerebrospinal fluid [25]. Serum interleukin (IL)-6 and IL-8 have been found to be elevated in patients who develop delirium [26], and IL-8 is increased in the CSF [27]. Delirium has been associated with disruption of the cortisol and beta-endorphin circadian rhythm in patients recovering from elective surgery [28]. It has been hypothesised that delirium is precipitated by pathologically elevated cortisol occurring with acute stress from illness or surgery [29].

It is recognised as an important cause of morbidity and mortality in dementia [8]. Delirium occurs in the course of dementia in about half to two-thirds of patients [8, 11, 18, 19] due to infections, the most common cause [11], and medications [30]. When associated with surgery, a number of factors could contribute to delirium such as hypotension, anaesthesia, hypoxia and hyponatraemia, and the elderly are particularly vulnerable to this condition. It is well known that it could follow focal lesions in the dominant hemisphere [2, 31, 32] with no lateralising neurological signs.

A number of precipitating factors have been put forward and more importantly include infections, metabolic disorders, drugs and intracerebral disease. Medications are the most common reversible cause of delirium [33, 34] (Table 1). The issue as to the manner how inflammatory signals arising from a systemic infection interact with stimuli that triggers

Table 1 Some of the precipitating factors of acute delirium

1. Infections
(a) Systemic – pneumonia, septicaemia, urinary tract infection
(b) Intracranial – meningitis, encephalitis
2. Drugs
(a) Sedatives – hypnotics, anxiolytics
(b) Anticholinergics
(c) Narcotic
(d) Alcohol and drug withdrawal
(e) Others
3. Metabolic, endocrine derangement
(a) Cardiac failure, respiratory failure, renal failure, disorders of electrolytes hypoglycaemia
4. Neurological
(a) Acute stroke
(b) Space-occupying lesions/raised intracranial pressure
(c) Head injury
(d) Epilepsy
5. Other
(a) Sensory impairment (vision/hearing)
(b) Urinary incontinence
(c) Faecal impaction
(d) Dehydration
(e) Sleep deprivation
(f) Surgery
(g) Immobilisation (restraints, catheters)

Information sources: Purdie et al. [33]; Moses and Van Kaden [34]; Fong et al. [36]

the delirium has gained significant importance [24]. According to MacLullich et al. [29], the triggers belong to two categories, 'direct brain insults' and 'aberrant stress responses'. The inflammatory signals that arise during a systemic infection evoke a co-ordinated sickness behaviour response [35]. Severe deleterious effects on brain function can result from systemic inflammatory signals in the elderly in the presence of neurodegenerative disease [24].

Clinical Manifestations

The clinical manifestations are sudden onset within 24–48 h, fluctuating severity with lucid intervals, marked distractibility and poor concentration, disorientation, recent memory loss, agitation, mood lability and minor psychiatric phenomena. In older people it could present with lethargy and decreased activity [10] or present with agitation, psychosis and withdrawal [37]. In a study of demented and non-demented elderly medical in patients, 19% had delirium, 41% of which had dementia, 41% were hyperactive,11.0% were hypoactive and 48% were mixed [38].

Delirium and dementia have been defined as different entities in the literature. Knowledge of the relationship between delirium and dementia which is the major cause of cognitive impairment in the elderly is scanty. Delirium may emerge in the course of dementia or may be the presenting symptom of the disorder. About two-thirds of patients with delirium occur in the course of dementia [8, 9]. Dementia may progress insidiously, and very often it is the delirium which may manifest acutely that brings the patient to the physician's attention.

It is generally assumed that the symptoms resolve in 1–2 weeks after appropriate diagnosis and treatment. Those who do not recover normal cognition may have undiagnosed dementia [39]. Delirium could however be more persistent than is usually realised. It is also not clear whether the occurrence of delirium leads to long-term cognitive impairment, and its natural history has not been clearly documented [11].

In a study half of the hospitalised patients with delirium required long-term placement in a nursing care facility. There was no deterioration in the functional status of delirium patients during hospitalisation [13]. Others found a decline at 3 months following discharge from hospital [40]. Another study revealed patients who had delirium in hospital became more dependant for activities of daily living on discharge from hospital, and patients who were not confused improved by discharge [15]. The functional disability following delirium rather than the cognitive decline together with the feeling among the caregivers that they may not cope was the significant factor that influenced institutionalisation. Non-demented patients with delirium showed more functional

decline, poor cognitive status and higher APACHE II score compared to those without delirium [38]. On the other hand, Margiotta et al. [38] found that in demented patients, there were no difference in cognitive status and APACHE II score among those with delirium and those without delirium.

Evaluation of Acute Delirium

Delirium is often missed or misdiagnosed because of the difficulties in diagnosis, and according to several workers, 30–70% of confused patients were unrecognised by clinicians [10, 18, 41]. It is misdiagnosed as dementia or psychiatric illness or misattributed as part of normal ageing [10]. The lack of awareness that confusion could be the sole manifestation of a life-threatening illness varied in its manifestations with multiple etiologies, and if the classical picture is not presented, the diagnosis is often overlooked. There is often a lack of appreciation of the fluctuating nature of the disorder [10]. A meticulous medical assessment includes a complete history and a physical and thorough neurological examinations. The history should include a drug history both for prescription and OTC medications and use of alcohol. It is important to recognise the difference between chronic and acute delirium. Delirium can be confused with dementia, depression and a psychiatric illness (Table 2). Those with multiple derangements are more likely to be confused (Fig. 1).

This is followed by psychometric testing. The Mini-Mental State Examination (MMSE) is helpful; the subscales, attention, concentration and recall, are the most sensitive. The Confusion Assessment Method may also be helpful [45] (Box 1). The cause should be investigated. The choice of laboratory tests should be based on the history and physical findings using the most accurate and discriminatory tests. The tests may include a full blood count, vitamin B12 and red cell folate levels, TSH/T4, liver function tests, urea, creatinine and electrolytes, urine analysis, culture and sensitivity testing. A chest X-ray and CT scan and a lumbar puncture were indicated.

Table 2 Differences between delirium and dementia

	Delirium	Dementia
Aetiology	Infection, metabolic, toxic, cerebrovascular	Neurological
		Degeneration
Onset	Usually rapid fluctuating course	Usually insidious
		Relatively stable
Course	Transitory, usually reversible	Slow progression
		Irreversible
Duration	Days to weeks	Permanent
Level of consciousness	Variably impaired	Unimpaired till late
	Hyperactive/ hypoactive	
Attention	Marked distractibility and poor concentration	Usually normal
		Until late stages
Orientation Memory	Disorientated varies	Usually impaired
		Short- and long-term memory impaired
Sleep	Sustained sleep deprivation	Fragmented sleep
	Sleeplessness at night	
Cause	Infection, medication, pain	Due to chronic disorder
	Intercurrent illnesses	Such as Alzheimer's disease

Information sources: Huang [43]; Lehman [44]

Box 1 The Confusion Assessment Method (CAM) Inouye [45]

1. Acute onset and fluctuating course
2. Inattention
3. Disorganised thinking
4. Altered level of consciousness

*The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.

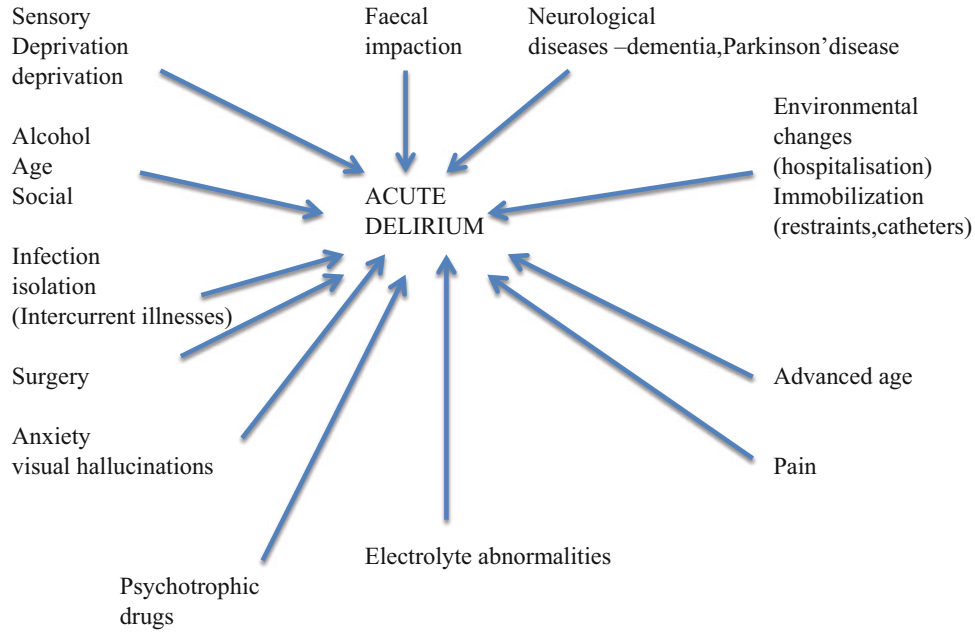

Fig. 1 Showing multiple derangements in delirium (Information sources: Fong et al. [36]; Elie et al. [42])

Management

Prevention of acute confusional state requires early detection and forceful management of the risk factors [46]. The primary aim is to identify and correct the underlying abnormality causing the delirium. Often this may not be possible. The next step is directed towards controlling the agitation and disruptive behaviours. Low-dose antipsychotic drugs can help to control agitation [37]. Neuroleptics and benzodiazepines have a role in the treatment of hyperactive subtype. Atypical antipsychotics often have some advantages over haloperidol [47]. Risperidone, olanzapine and quetiapine have been shown to be as effective as haloperidol and are reasonably safe with fewer extrapyramidal effects than haloperidol [48]. Hypotension has been reported to occur occasionally with risperidone and quetiapine, and occasionally olanzapine can worsen the delirium [48]. If the delirium is associated with alcohol, thiamine has to be administered during the acute stage. Physical restraint should be used only as a last resort to maintain patient safety. Concurrently, supportive and restorative care should be provided. The patient should be nursed in single quiet room with good lighting to maintain a normal sleep pattern. Fluid and nutritional needs need to be attended to. Monitoring should be done during day and night, and there should be continuity of care by the staff and a calm approach. Relatives and friends should be encouraged to help maintain a calm environment [8, 37].

Impact

Acute delirium is common and has an immense impact on the health of older people and a burden on family members [49]. It is often a life-threatening condition in the elderly and associated with increased risk of mortality whilst in hospital [50], long-term cognitive deficits [49, 51] or dementia [51]. It is associated with prolonged

hospital stay [52] with increased health-care costs and increased rate of institutionalisation [50, 51]. Delirium is a frequent complication in the elderly surgical patients with an incidence ranging from 37% to 74%, and post-operative delirium has been shown to precede long-term complications such as dementia [53]. It is a frequent complication of older intensive care unit (ICU) patients and often continues past their ICU stay [54] and a 10% increase risk of death [49]. It incurs enormous costs to both patient and the health-care system [55], and in the United States, it is estimated to increase the health costs by US $2500 per patient totalling $6.9 billion per year [56].

Box 2 Key Points: Acute Delirium

- Delirium is a disorder of reduction and erratic shifting of attention [2].
- The elderly are particularly vulnerable.
- Infections [1] followed by medications are common causes [30, 33, 34].
- About half to two-thirds of patients with delirium occur in the course of dementia [8, 11, 18, 19].
- Those with multiple derangements are likely to be confused.
- About 30–70% of patients with delirium were unrecognised by clinicians.
- Delirium is often missed or misdiagnosed, often misdiagnosed as dementia or a psychiatric illness [10, 18, 40].
- Old people could present with lethargy and decreased activity [10].
- The subscales in MMSE, attention, concentration and recall, are the most sensitive.
- The Confusion Assessment Method may also be helpful [45].
- The primary aim is to identify and correct the underlying abnormality.
- May require psychotropic drugs. Concurrent supportive and restorative care should be provided.

Box 2 Key Points: Acute Delirium (continued)

- Increased rate of hospitalised patients with delirium requires long-term placement in a nursing care facility [50, 51].
- Delirium may be life-threatening and failure to recognise and treat will cause increased morbidity and mortality.

Multiple Choice Questions

1. In acute delirium which of the following is unlikely?
   A. The hallmark of delirium is the reduction of attention.
   B. It is often misdiagnosed as dementia or a psychiatric illness.
   C. About one-half or two-thirds of patients with delirium occur in the course of dementia.
   D. Medications are not an important cause of delirium.
2. Which of the following is not suggestive of acute delirium?
   A. Sudden onset
   B. Fluctuating course
   C. Preserved sleep-wake cycle
   D. Variability in cognitive testing
3. In the diagnosis of acute confusional state, the following are true, except:
   A. The elderly could present with lethargy and decreased activity.
   B. Special attention should be given to attention, concentration and recall on the MMSE subscale.
   C. CAM is helpful.
   D. Diagnosis is rarely a problem in clinical practice.
4. In the management of delirium, the following are true, except:
   A. May require psychotropic drugs.
   B. There should be continuity of care day and night by the staff.
   C. Physical restraints is routinely required.
   D. Relatives and friends should be encouraged to help and maintain a calm environment.

MCQ Answers

1 = D; 2 = C; 3 = D; 4 = C

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The Dementias

67

Contents

Abstract

DSM-5 has replaced the term "dementia" with "major neurocognitive disorder (NCD) or mild neurocognitive disorder" but accepts "dementia" as an agreeable alternative. The purpose of this change is to lessen the stigmatization associated with the word "dementia" toward elderly individuals and to bring the diagnostic guidelines in step with the present-day practice. The DSM-5 details six cognitive domains, namely, attention, executive function, learning and memory, language, perceptual-motor function, and social cognition. It is estimated that 2% and 10% of dementia begin before the age of 65, according to the World Alzheimer Report and is referred to as early-onset dementia.

Keywords

Dementia · Alzheimer disease · Major neurocognitive disorder · Early-onset dementia · Late-onset dementia

Introduction

Current demographic findings predict an increase in the elderly population more so the very elderly, and this trend is likely to continue. This means that the number of dementia patients and those with other age-related neurological disorders will increase [1]. In 2010, there were nearly 5.5 million Americans aged 85 or older [2], and this number is expected to triple or quadruple by the middle of the century [3]. In Europe, dementia is more common than stroke in terms of both incidence and prevalence [4]. In the United States, age-specific prevalence estimates indicate that 4.7 million individuals aged 65 years and over had Alzheimer's disease (AD) dementia [5]. Of these 1.8 million were 85 years or older, and the total number with AD dementia in 2050 is projected to be 13.8 million, with 7.0 million aged 85 years or older demonstrating the magnitude of the problem [5]. The prevalence and incidence rates for dementia across Asia, China, Europe, and the

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_70

United States are comparable, but the types of dementia tend to vary. Cerebrovascular disease is a relatively important cause in East Asia than in Western countries [6]. In most Asian countries, the age-adjusted estimates of dementia prevalence are above 5% but are much lower in India (1–3%) and sub-Saharan Africa [7].

Men and women are equally at risk, and there was no difference in sex regarding Alzheimer's disease prevalence [8, 9], but some studies have reported higher figures for women in the most advanced ages [10, 11]. More women are affected since Alzheimer's disease is a disease of the elderly, and women have a longer average life span than men. In another study, the differential incidence by type of dementia found the incidence patterns by age were similar between Alzheimer's disease and vascular dementia but not by gender [12].

In 2013, the American Psychiatric Association published its fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [13]. What was classified as "delirium, dementia, amnestic, and other cognitive disorders" in DSM-IV is now called "neurocognitive disorders." DSM-5 has replaced the term "dementia" with "major neurocognitive disorder (NCD) or mild neurocognitive disorder" but accepts "dementia" as an agreeable alternative. The purpose of this change is to lessen the stigmatization associated with the word "dementia" toward elderly individuals and to bring the diagnostic guidelines in step with the present-day practice [14]. However, if the physician prefers, the dementias can still be referred to by their accustomed names, for example, Alzheimer's dementia, vascular dementia, or frontotemporal dementia [15], and in fact DSM-5 has included "or dementia" in parentheses when referring to major NCD [14].

Differential Diagnosis

A number of different categories have evolved to define cognitive deficits especially memory in elderly people who in spite of their impairments do not satisfy the criteria for dementia. Dementia must be differentiated from age-associated memory impairment (AAMI) which may involve not only memory but other cognitive functions and with a negative effect in daily life activity which is within the age-associated norms of cognitive performance. It seems to be more frequent with affective disorders from low sociocultural status [16]. There is no progression however toward cognitive decline characteristic of dementia [17]. Another is mild cognitive impairment (MCI). Patients with MCI perform relatively poorly on formal tests of memory and often show mild difficulties in other cognitive functions to an extent beyond that expected for age and individual background. Individuals who meet the criteria for MCI are at a greater risk than those with AAMI to develop dementia. Depression is known to cause cognitive symptoms. Chronic substance abuse can induce persistent dementias. If suspected of causing or contributing to the cognitive impairment, ceasing the drug or substance is justified.

Diagnosis

The American Psychiatric Association defined dementia as a disorder characterized by a decline in cognition involving one or more cognitive domains. The DSM-5 details six cognitive domains, namely, attention, executive function, learning and memory, language, perceptual-motor function, and social cognition. The deficits represent a decline from previous level of function, leading to an incapacity for independent activity. It poses special difficulties with behavioral and psychological symptoms and debilitating psychological distress that caregivers may experience. Major NCD in DSM-5 is determined by:

(1) Evidence of substantial cognitive decline from a previous level of performance in one or more of the domains outlined above and the decline in neurocognitive performance involving test performance in the range of two or more standard deviations below appropriate norms on formal testing or equivalent clinical evaluation [18].

(2) The cognitive deficits are sufficient to interfere with independence.
(3) The cognitive deficits do not occur in the context of a delirium.
(4) The cognitive deficits are not attributable to another mental disorder [18].

Memory impairment is not a strict condition of major NCD. In the case of mild NCD, there should be a modest cognitive decline from a previous level of performance in one or more of the cognitive domains outlined above, and these cognitive deficits must be insufficient to interfere with independent daily activities. The DSM-5 has the advantage of including personality change as well as higher cognitive deficits as well as focusing attention specifically in excluding other conditions that may mimic dementia, for instance, it included an intact arousal mechanism to distinguish dementia from one with a delirium. It provides a key to the identification of dementia but not the cause [19]. The Barthel Index [20] commonly used as a rating scale of physical dependency could be used in a shorten form.

Mental status examinations are capable of differentiating between the presence and absence of significant cognitive impairment. The cognitive changes that occur can be indexed by measures of global cognitive scales such as the Mini-Mental State Examination (MMSE) [21]. There is no lack of clinical scales. The MMSE is a clinical scale designed for screening, diagnosis, and serial assessment of geriatric patients and is a relatively comprehensive measure of cognition including orientation, memory, concentration, language, and design copying, but it lacks to assess perceptual ability and abstract thinking and may be supplemented by such items as the ability to abstract, calculate, and perceive.

DSM-5 removed the subcategories "early onset" (onset at age 65 years and below) and "late onset" specifying that since there is no difference in the underlying pathology, the differentiation into early and late onset has little scientific grounds for retaining this distinction. In this chapter, this distinction is retained, for evaluating the oldest old with cognitive impairment requires special consideration of the features of dementia unique to the 90 years and older population [22]. Furthermore there are challenges of diagnosing dementia in the oldest old, and the prevalence for dementia in those 85 years and over ranges from 18 to 38% [23]. Hence a wider differential diagnosis is necessary for early-onset dementia compared to late-onset dementia [24]; about 12% of the population over 65 are the oldest old which is the fastest-growing segment of the population [25].

It is estimated that 2% and 10% of dementia begin before the age of 65, according to the World Alzheimer Report [26] and is referred to as early-onset dementia [27]. Dementia occurs in several neurodegenerative disorders and is presently characterized by neuropathological criteria, most distinctly Alzheimer's disease (AD), frontotemporal dementia (FTD), Lewy body dementia (LBD), and hippocampal sclerosis (HAS) [28]. The most common type (the late onset) is that which occurs in people aged 65 years or over. Dementia mainly manifests in older populations; however, there is an increasing recognition for dementia cases that begin before the age of 65 years [26]. The population rate of early-onset dementia (EOAD) in Alzheimer's disease is 1–2% [29]. Approximately 5.2 million Americans have AD of which approximately 200,000 are younger than 65 years [30]. Early-onset dementia is often misdiagnosed, for it has a more varied differential diagnosis [31, 32]. Other reasons for the misdiagnosis or delayed diagnosis are the varied presentation. For instance, early-onset AD may have notable cognitive deficits apart from memory loss and potential familial history with neurological features such as spastic paraparesis, seizures, and myoclonus [32]. Furthermore neuropsychiatric features may predominate in EOD [32]. Another reason being that in many the presence of comorbid diseases such as cardiovascular risk factors may influence the clinical presentation [24]. Table 1 shows some of the differences between early-onset and late-onset dementia.

The prevalence of FTD has been estimated in 15 per 1000,000 patients between 45 to 64 years of age [33], and vascular and FTD are the second most common form of early-onset dementia after AD with early age of onset ranging from 45 to

Table 1 Some differences between early-onset, late-onset, and oldest old dementia

	Early onset	Late onset	Oldest old
Age	<65 years	>65 years	>85 years
Gender M:F			F > M
Incidence and prevalence rates	4–5% usually sporadic		90–94 years 12.7% per year
			95–99 years 21.2% per year
			100+ 40.7% per year
Genetic susceptibility	APOE*e*2 5% autosomal dominant with mutations in PS1, PS2, and APP genes	APOE*e*4	APO less relevant
Pathology	Left parietal changes, right parietal changes, and occipital changes		
Clinical presentation	Non-amnestic in 64% deficits in language, visuospatial and praxis or	Cognitive memory other non-memory cognitive profile	Age-related cognitive decline-executive functions and mental speed
Neuropsychological	Executive functions, attention	Worse confrontation naming and verbal recogition memory	
Course and rate of progression	More aggressive		Slow progress
	Rapid cognitive		
	Deterioration		

Information sources: Gardner et al. [23]; Kawas and Corrado [25]; Panegyres and Chen [27]; Mendez [32]; Corrado et al. [38]; Mendez [39]; Mendez [40]; Koedam et al. [41]; Smits et al. [42]; Kaiser et al. [43].

65 years [34]. Early-onset Lewy body spectrum disorders have been described although rarer than AD and FTD in patients younger than 65 years [24]. AD, FTD, and vascular dementia are the three common causes of young-onset dementias [35]. Other causes include traumatic head injury, alcohol-related dementia [32, 36], and Huntington's disease [36]. Snowden et al. [37] examined the diagnostic accuracy of early-onset dementias and found that 46% had a clinical diagnosis of one of the syndromes of FTD, 46% were diagnosed as AD, and the remaining had dementia with Lewy bodies, Creutzfeldt-Jakob disease, vascular dementia, or unclassified dementia and concluded that dementias can be distinguished in life with a high level of accuracy.

Dementia is a common disease, and most general practices will include a significant number of demented patients. It can pose problems in diagnosis more so in the mild end of the spectrum. Several studies have shown that the primary care physicians identify only a segment of the cases [44–48]. Some of the reasons for failure to diagnose or underdiagnose dementia in a fair proportion of patients by the primary care physician could be attributed to a fear of committing to a diagnosis, lack of confidence on their diagnostic ability, lack or inadequate knowledge, referral routines, lack of awareness of current practice requirements, and time-consuming diagnosis [47–49], for few primary care physicians perform routine assessments and misclassified diagnoses [48, 50].

The degree of cognitive impairment and the severity of functional impairment are the basis to say that a patient has dementia. The diagnosis of dementia results from a comprehensive evaluation which includes a history obtained from different sources substantiated by a reliable informant and should aim at specific cognitive, behavioral, and

Table 2 Assessment of activities of daily living

Personal self-care Feeding oneself Bathing Toileting Mobility Able to move from bed to standing position or to a chair Able to walk (with or without assistive devices) or use wheel chair Continence Continent of urine always or rarely incontinent or frequently or usually continent Continent of feces	Within the home Cooking Housecleaning Laundry Management of medications Management of telephone Outside the house Shopping for food, clothing, drugs, etc. Use of transportation travelling to necessary and desired activities (e.g., physician's appointment, religious, or social events

mood changes and on symptoms relating to medical, neurological, and psychiatric illnesses. Drugs should be reviewed and a family history of dementia, depression, stroke, or related conditions obtained. The clinical history should include an evaluation of the patient's functional abilities in his activities of daily living (ADL) and instrumental activities of daily living (IADL). The latter is affected in the early stages (Table 2).

A thorough physical and neurological examinations followed by mental status are essential screening which includes assessment of cognitive and affective states are essential. The Mini-Mental State Examination is easy to use. These may be supplemented by additional tests for abstraction (proverb, metaphor) and judgment and for right hemispheric function (clock drawing, geometrical figures) and parietal lobe function (left-right discrimination, identifying fingers, objects by touch alone, construction of square with match sticks) (Box 1). Hematological and biochemical investigations involve complete blood count, tests for thyroid function, and vitamin B12 level screening for infectious disease such as neurosyphilis. Neuroimaging (computed tomography, CT; magnetic resonance imaging, MRI) of the brain is used to exclude structural lesions (such as cerebral tumors, normal pressure hydrocephalus, cerebral infarction, subdural hematoma) that may subscribe to dementia. As with laboratory investigations, the yield is low [51]. Figure 1 suggests an algorithm for dementia diagnosis.

Box 1 Additional Mental Tests

1. Abstraction (proverb,metaphor)
2. Judgment (responding decision requiring situations
   (seeing a fire in the house)
3. Visuospatial (right hemispheric function) drawing a clock
4. Parietal lobe function
   Show left hand; touch left ear with right hand
   L-R discrimination
   Identify object(coin, key) by touch alone (stereognosis)
   Demonstrate normal 2 point discrimination
   Construct square with matches

Having made a diagnosis of dementia, it is important to identify the type of dementia, for instance, pharmacological agents may behave differently in different dementias. The search for the type of dementia includes the clinical setup and a number of additional examinations which may reveal causes that were not suspected on clinical grounds, and moreover mixed dementias may be of concern. It is often difficult to differentiate the causes because they are so ill-defined, and confirmation is only possible by postmortem pathological examination. Box 2 summarizes the main features of the common types of dementia.

Box 2 Differential Diagnosis of Dementia

- Alzheimer's disease
  - Insidious onset and gradual progressive decline
- Vascular dementia
  - Cerebrovascular risk factors,history of strokes, stepwise deterioration,

(*continued*)

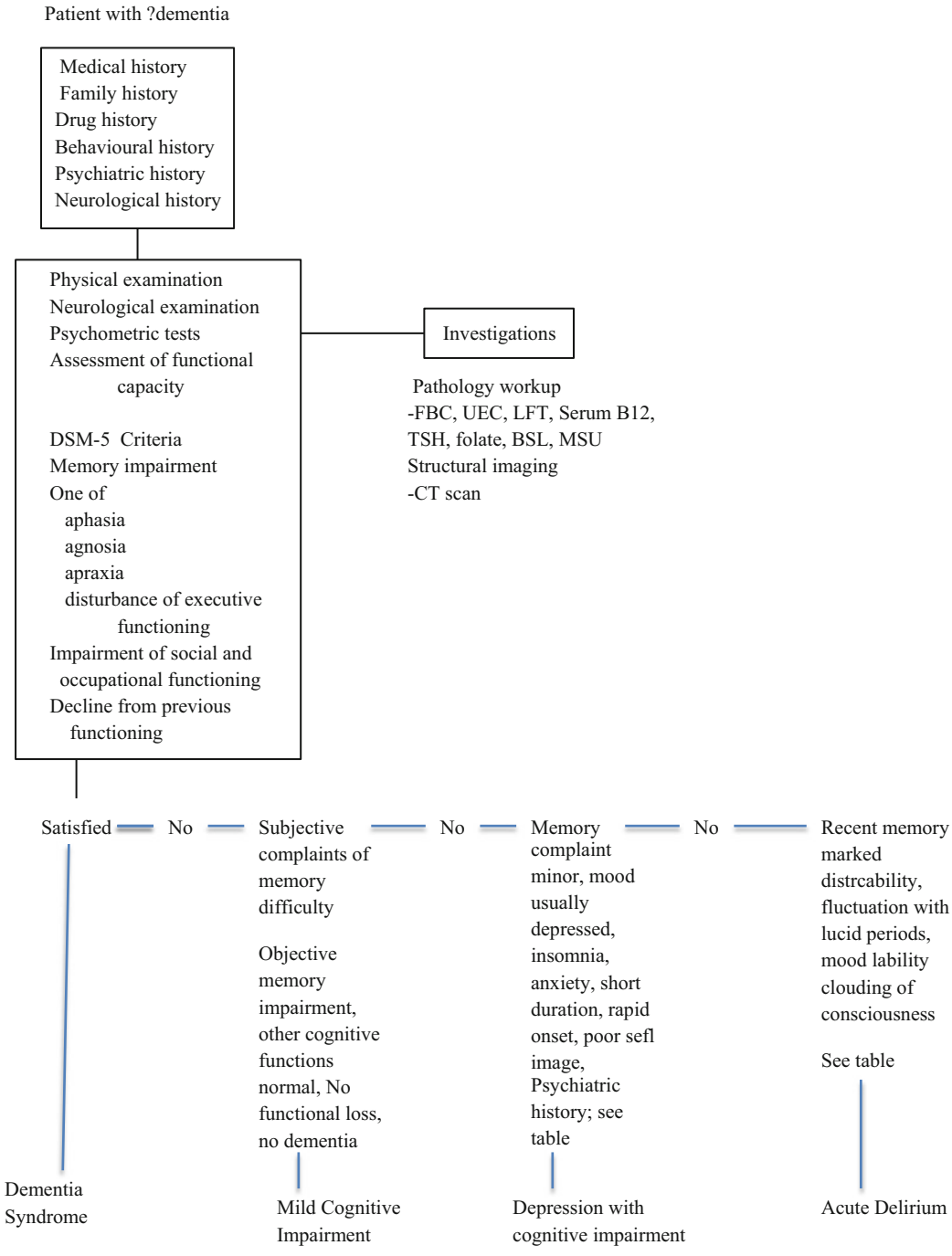

Fig. 1 Diagnosis of Dementia

Box 2 Differential Diagnosis of Dementia (continued)

fluctuating course, focal signs, abnormal scan

- Dementia with Lewy bodies
  - Parkinsonism, visual hallucinations, neuroleptic sensitivity
- Frontotemporal dementias
  - Personality change, poor judgment, intact memory

Impact

Dementia is a chronic progressive disease and is characterized by a decline in the cognitive, behavioral, and social domains, leading to an incapacity for independent activity. Dementia affects all aspects of the patient's life. Functional status is markedly impaired. Activities of daily living (ADL) are affected even in patients with mild dementia. It poses special difficulties with behavioral and psychological symptoms and disturbing, disruptive, and dangerous behaviors with devastating consequences for the patient and families [52]. The severity of behavioral disorders and duration of the dementia correlate with the QoL of caregivers [53]. Caregivers may experience and are at high risk of psychological distress resulting in breakdown in care [54]. Depression and anxiety have been reported among caregivers and correlated with hours of care, physical, and psychological illness [55].

Alzheimer's disease and related dementias affect quality of life (QoL) in many ways [56]. In the past decade or two, there have been considerable interest and emphasis on the quality of life as a primary objective in the treatment of dementia [56], to preserve or to improve quality of life [52] both for the person with dementia and family caregivers. The factors that affect QoL for patients with dementia reporting their own QoL and family caregivers reporting their care recipient included mood, engagement in pleasant activities, and ability to perform ADLs and in addition physical and cognitive functioning by family caregivers [56]. Hence necessary determinants for acceptable QoL would be a cheerful mood, taking part in pleasant activities, preservation of ADL, mobility, and cognitive ability [56] Box 3.

Box 3 Key Points. Dementias

The American Psychiatric Association defined dementia as a disorder characterized by a decline in cognition involving one or more cognitive domains.

The DSM-5 details six cognitive domains, namely, attention, executive function, learning and memory, language, perceptual-motor function, and social cognition **and** special difficulties with behavioral and psychological symptoms.

It is estimated that 2% and 10% of dementia begin before the age of 65, according to the World Alzheimer Report [26], and is referred to as early-onset dementia [27].

Having made a diagnosis of dementia, it is important to identify the type of dementia, for instance, pharmacological agents may behave differently in different dementias.

- The diagnosis can pose problems more so in the mild end of the spectrum.
- The degree of cognitive impairment and severity of functional impairment form the basis to say the patient has dementia.
- The family physician is often the first point of contact for most patients and source for specialist referral and support services.

Multiple Choice Questions

The following are true of dementia disorders, *except*:

A. The diagnosis can pose problems more so in the mild end of the spectrum.

B. It is estimated that 40% of dementia begin before the age of 65 and is referred to as early-onset dementia.
C. The degree of cognitive impairment and severity of functional impairment form the basis to say the patient has dementia.
D. Activities of daily living (ADL) are affected even in patients with mild dementia.

MCQ Answers

1 = B

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Neurodegenerative Disorders

68

Contents

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_71

Abstract

Alzheimer's disease primarily a neurodegenerative disorder is the commonest cause of dementia followed by vascular dementia. Alzheimer's disease is a disorder of the amyloid precursor protein (APP), the frontotemporal (FTD) syndromes and some of the extrapyramidal dementias (corticobasal, progressive supranuclear palsy) are associated with the microtubule – associated protein tau. Other degenerative diseases including Parkinson's disease, multiple system disease and Lewy Body dementia are associated with a – synuclein. The review provides an overview of the neyodegenerative dementias.

Keywords

Alzheimer's disease · Lewy body dementia · Amyloid precursor protein · The frontotemporal (FTD) syndromes · Extrapyramidal dementias

Introduction

In a European study the incidence rates for possible and probable Alzheimer's disease the most common form of dementia adjusted for age, sex and education was 1.2 per 1,000 person years for 65 year old and 63.5 per 1,000 person years for those above 90 years [1]. Alzheimer's disease primarily a neurodegenerative disorder is the commonest cause of dementia followed by vascular dementia [2]. The degenerative dementias are now being reclassified according to the associated protein abnormalities although this classification does not necessarily help in the diagnosis but may facilitate development of strategies for the disease treatment and prevention [3] (Box 1).

Box 1 Classification Based on Protein Abnormalities

Diagnosis	Protein involved
Alzheimer's disease	Amyloid precursor protein
Fronto-temporal dementia	Tau
Cortico-basal degeneration (CBD)	Tau
Progressive supra-nuclear palsy(PSP)	Tau
Parkinson's disease	x-synuclein
Multi-system athropy (MSA)	x-synuclein
Dementia of the Lewy body type	x-synuclein

Information sources:Goedert [5], Kowlaska [6], Morris et al. [7], and McKeith et al. [8].

Alzheimer's disease is a disorder of the amyloid precursor protein (APP), the frontotemporal (FTD) syndromes and some of the extrapyramidal dementias (corticobasal, progressive supranuclear palsy) are associated with the microtubule – associated protein tau. Other degenerative diseases including Parkinson's disease, multiple system disease and Lewy Body dementia are associated with a – synuclein. Neurofibrillary lesions made up of microtubule associated with protein tau is not only limited to Alzheimer's disease but also characterizes a heterogenous group of neurodegenerative disorders and clinically distinguished by dementia or/and motor symptoms [4] and grouped together under the general term taupathies [5]. In DSM-5 the subtypes are shown in Box 2.

Box 2 Subtypes of Neurodegenerative Disorders (NCDs)

Major or Mild Neurocognitive Disoders due to Alzheimer's Disease
Major or Mild Frontotemporal Neurocognitive Disorder
Major or Mild Neurocognitive Disorder with Lewy Bodies
Major or Mild Vascular Neurocognitive Disorder
Major or Mild Neurocognitive Disorder due to Traumatic Brain Injury
Substance/Medication-Induced Major or Mild Neurocognitive Disorder
Major or Mild Neurocognitive Disorder due to HIV Infection
Major or Mild Neurocognitive Disorder due to Prion Disease
Major or Mild Neurocognitive Disorder due to Huntington's Disease
Major or Mild Neurocognitive Disorder due to Another Medical Condition
Major or Mild Neurocognitive Disorder due to Multiple Etiologies
Unspecified Neurocognitive Disorder

Information sources: Alzheimer's Australia [9].

Alzheimer's Disease (Major or Mild Neurocognitive Disorder Due to Alzheimer's Disease)

The history of senile dementia dates back to ancient Greek and Roman physicians and philosophers [10]. In the ancient Indian medical system Ayurveda, geriatric and cognitive function and Sanskrit names such as Cittanasa for dementia were well recognised [11]. In 1906 Alois Alzheimer a German neuropathologist and clinician described a case report of a 51-year old woman who presented with paranoia, memory disturbance, aggression, confusion and progressive sleep [12] and pathological study revealed the presence of neurofibrillary tangles and senile plaques [13]. A specific disease distinct from senile dementia was thought to have been shown by Alzheimer in his seminal paper in 1907 [14]. Emil Kraepelin coined the eponym Alzheimer's disease. Hereinafter senile dementia evolved from an ill-defined concept occurring in old age to become a defined clinical-pathological entity.

Alzheimer's disease (AD) is a neurodegenerative disease characterised by progressive loss of memory and other cognitive functions, and inability to perform basal activities of daily living together with behavioural and psychiatric symptoms. In one study neither the age- specific incidence of Alzheimer's disease nor the morbidity due to Alzheimer's disease differed significantly [15]. The EURODEM reported a higher incidence of Alzheimer's disease in women and suggested sex as a risk factor for AD [1]. It is still unclear whether the higher incidence in women is due to the higher risk or to the longer life expectancy in women.

The hallmarks of AD are the extracellular accumulation of amyloid beta (Abeta) peptides forming the core of the senile plaques and intracellular neurofibrillary tangles (NFTs) made up of the microtuble associated tau protein in a hyperphosphorylated state [5]. This diminishes its ability to bind to tubulin resulting in destabilization of the microtubule structure [16]. The primary function of tau is its ability to interact with alpha- and beta-globulin and stabilize the microtubules [17]. Free tau fractions are elevated when tau is hyperphosphorylated [18]. The hyperphosphorylated tau aggregates into oligomers to form paired helical filaments (PHFs) to generate NFTs [19] and several protein kinases are involved in this process [20]. GSK-3 beta (glycogen synthase kinase 3 beta) is an important tau kinase and is overactive in AD and has been shown to hyperphosphorylate in transgenic mouse models in AD [21]. Abetapeptide arises from a large precursor, the amyloid peptide precursor (APP) and there two identified catabolic pathways for APP [22]. In the amyloidogenic pathway of APP, APP is cleaved by secretase enzymes

and neurotoxic Abeta peptides are released and amass into oligomeric aggregates [17] and induces neuronal apoptosis [22]. In the non amyloidogenic pathway APP is cleaved preferentially by beta-secretase [23] within the sequence of the amyloid peptide and hinders the formation of the full length Abeta found in the core of senile plaques [22].

Whilst the mechanism in AD is unclear several hypothesis have been postulated [24]. According to the amyloid cascade hypothesis accumulation of senile plaques made primarily by deposits of Abeta peptide in the initiating lesion in AD [25] and is due either to their increased production or decreased clearance of Abeta peptides [26] although the presence of tangles is essential to dementia [27]. The accumulation of Abeta is the main cause of neuronal degeneration and induces accumulation of tau in the AD brain [26]. Alternative hypothesis is the cytoskeletal changes that arise from the hyperphosphorylation of Tau leads to a cascade of events and finally cause neuronal death [23]. Neither cascade explains adequately the diversity of pathological processes underlying the disease [23, 24]. The Abeta deposits involve the neocortex while the intracellular tau accumulation manily affect the hippocampal regiin [28].

Age at onset of AD have been used to differentiate subtypes with 65 years arbitrarly used to distinguish the early from the late- onset [29]. However age cut off at 70 was found to differentiate better between early and late- onset than 65 years [30]. An estimated 5.2 million Americans have AD and approximately 200,000 are under the age of 65 years and comprise the younger onset [9]. Early-onset familial subtype occurs before the age of 65 years and is due to mutations in the genes presenilin 1 and 2 and the gene for amyloid precursor protein [31–34]. The genetic defects have been identified on chromosomes 21, 19, 14, 12, and 1. Of the early onset cases of AD less than 1% of the cases are linked to chromosome 21. presenilin 1 (PSEN1) on chromosome 14 is the most common and presenilin 2 (PSEN2) on chromosome 1 least common [31, 33, 35].

Clinical Manifestations

AD patients most commonly present with gradual progressive memory loss together with time other domains of cognitive impairment such as visuospatial skills and executive functions and behavioural symptoms. They may also have language disorders for example progressive aphasia and anomia. Less commonly AD can present as a focal syndrome with signs locallised to one anatomical region. Crystal et al. [36] described a 57-year old woman with progressive right parietal disorder chatacterised by astereognosis and pseudoathethosis and 2 years later manifested intellectual deterioration. Biopsy had revealed numerous plaques and tangles. Other presentations include impaired visuospatial skills with progressive visual loss [37] and slowly progressive hemiparesis [38] and proven pathologically. Behavioural and psychological symptoms are also common in AD. Apathy, agitation, aggressiveness, motor restlessness, delusions and hallucinations may develop (Box 3).

Box 3 Alzheimer's Disease

Usually after the age of 65 years.

AD patients most commonly present with gradual progressive memory loss together with time other domains of cognitive impairment such as visuospatial skills and executive functions and behavioural symptoms.

In predicting outcome-four groups – benign – little or no progression, myoclonic- severe intellectual decline and frequent mutism after younger onset; extrapyramidal- severe intellectual and functional decline and frequent psychotic symptoms; typical – a gradual progression of intellectual and functional decline [43].

Numerous studies have indicated differences in the clinical characteristics between early- onset Alzheimer's disease (EOAD) and late- onset Alzheimer's disease (LOAD) particularly in symptoms and clinical course [44].

AD usually is most prevalent after the age of 60. Some forms of familial early-onset AD can appear as early as the fourth decade. The early- onset dementia has been associated with more severe language disorder [29, 39]. Although 45% of the patients had familial history relative familial risk could not be demonstrated based on age of onset or aphasia [29]. Early onset AD has a more aggressive course, shorter survival more rapid cognitive decline as well as greater frequency of language disturbance [40]. Parkinsonian signs characterized by rigidity, orofacial dyskinesia, akinesia and diminished associated movements were seen in 61% and 92% of dementia patients [41, 42].

According to Mayeux et al. [43] certain clinical manifestations may be useful to in predicting outcome. In their study of Alzheimer;'s disease patients they found four groups – benign – little or no progression, myoclonic- severe intellectual decline and frequent mutism after younger onset; extrapyramidal- severe intellectual and functional decline and frequent psychotic symptoms; typical – a gradual progression of intellectual and functional decline. Numerous studies have indicated differences in the clinical characteristics between early- onset Alzheimer's disease (EOAD) and late- onset Alzheimer's disease (LOAD) particularly in symptoms and clinical course [44]. The conventional dividing line between both is 65 years [44]. The differences between EOAD and LOAD are summarised in Table 1.

Table 1 Differences between early and late-onset Alzheimer's disease

	Early-onset Alzheimer's disease	Late-onset Alzheimer's disease
Age of onset	>65 years	<65 years
Gender	M>F	F>M
Risk factors		
Family history	++	
Genetic	5% of total A, PSEN1,PSEN2, APP	APOE epsilon4
Clincal features		
	Nonamnestic	Amnestic
	Deficits in language, visuospatial, executive and attention myoclonus	Memory -visual and orientation
Neuropsychiatric	++	Family history of depression in depressed LOAD
Neurochemical changes	+++	++
Structural brain abnormalities	Neocortical and temporal widespread loss of neurones	Limbic areas
Prognosis	More aggressive, shorter survival time	

Information sources: Panegyres and Chen et al. [27], Mendez [40], Sa et al. [44], Panza et al. [45], Devi et al. [46], and Iversen [47]

Hippocampal Sclerosis of Aging

Based on the pathologic criteria Hippocampal sclerosis of aging (HS-Aging) is defined as neuronal loss and gliosis in the hippocampal formation that is out of proportion to AD-type pathology [48, 49]. It is most common in patients over the age of 80, in the oldest old autopsy studies have shown that 5–30% of the 90+ had HS-Aging [48, 50, 51]. The association between HS-Aging, Alzheimer's disease and Fronto-temporal dementia is unclear and the manifestations of HS-Aging indicate that it is probably a separate disease [52]. It is strongly associated with TDP-43 pathology [48, 49], in 86% [50]. TPD-43 pathology in the basal forebrain is strongly associated wth HS-Aging [53]. HS-Aging affects a small propportion of those diagnosed as probable AD and the presence of HS-Aging pathology with significant cognitive impairment has often been misdiagnosed as AD clinically [48]. Both HS-Aging and an ABCC9 gene variant have been associatd with moderate or severe arteriosclerosis in the very old [51].

Fronto-temporal Dementia and Other Focal Atrophies

Cortical lobar atrophies are more common than realized. Localized cerebral atrophy refers to a group of degenerative disorders that present with distinctive clinical and neuropsychological features and have a high genetic element. It is debated whether some of them are part of a diffuse disease or in fact they distinct entities.

Frontotemporal Dementia (Major or Mild Frontotemporal Neurocognitive Disorder)

Prominent involvement of the frontal and temporal lobes give rise to frontotemporal dementia (FTD). FTD/Pick complex now refers to a group of diseases which include Pick's disease, Fronto-Temporal Lobar Degeneration (FTLD), Primary progressive Aphasia (PPA), Semantic Dementia and Cortico-Basal Degeneration (CBD) [54]. FTD has also been described with Motor Neurone Disease (MND) [55], Corticobasal degeneration, Progressive supranuclear palsy [56] and atypical Parkinsonian syndromes. All these conditions could be considered as Fronto-Temporal Dementia, a part of Pick's complex. FTD accounts for about 10–15% of all dementias [6]. FTD primarily occurs between the ages of 45 and 65 years. There is a family history in about 40% and autosomal dominant inheritance in about 20% [57, 58, 59].

Aberrant mutation of tau protein is the fundamental neuropathological finding in FTD and this altered protein destabilises the microtubule structure [7]. FTD with tau positive inclusions and includes PSP, CBD, Pick's disease and mutation of the microtubule-associatd protein tau (MAPT) gene on chromosome 17(ETDP-17) [60]. The first mutation of the tau protein responsible for FTD and parkinsonism is linked with chromosome 17 (FTDP-17) [6]. Ubiquitin-postive, FTD with tau negative inclusions are common finding in FTD and included with progranulin gene mutations [61]. It has been recognised that there ia a clinical overlap between FTD and amyotrophic lateral sclerosis (ALS) and is characterised by neuronal inclusions that are immunoreactive to ubiquitin but not to tau and this pathogenic protein has been identified as TDP-43 [62–64].

Clinical Manifestations

Emphasis on other lobes has led to two patterns of presentation, frontal variant with gradual changes in behaviour and the temporal variant with gradual progressive language dysfunction. The former, behavioural variant could present with personality changes, loss of insight [65], disinhibition or with apathy, disinterest and unconcerned. The symptoms of disinhibition may simulate a personality disorder or manic psychosis. The lack of inhibition results in impulsive or inappropriate behavior with behavioral irregularities such as pilfering, shoplifting, swearing, undressing or urinating in public places. They lack concern over personal appearance and prone to overeating with food fads. Even though there are complaints of memory problems they rarely have true amnestic syndrome (Table 2).

The temporal variant or language variant is characterized by early and progressive change in language function and occurs in a setting of relative preservation of other cognitive domains such as memory [66]. The language variability is referred to as primary progressive aphasia (PPA) and is further subdivided as progressive non-flent aphasia [67, 68] and semantic dementia [67]. The language dysfunction could take the form of a progressive non-fluent aphasia, impaired syntax, poor repetition, preserved comprehension and relatively preserved performance in other neuropsychological functions. By contrast others can present with anomia and persuasive semantic deterioration which may disrupt language and memory. With progression the patient becomes virtually mute. A third language variant has been described unlike that of the the other two [69] and notable feature is there is profound impairment for reptition of sentences with difficulties in understanding intricate sentences [69]. It has been suggested that this variant may be an atypical presentation of AD [70, 71] and the pattern of atrophy seen is involvement of the left temporoparietal junction [72] and a smaller

Table 2 Frontotemporal dementia

	45–65 years
	Family history (50%)
	Mean duration of illness 8 year (10–15 years)
Frontal	
(1) Disinhibited overactive, unconcerned inappropriate behaviour	(2) Apathetic, inert, lack of drive, little response to stimuli, wandering, altered food intake
Stereotyped behaviour	
Temporal	
Economy of speech output (dynamic aphasia) pressure of speech, repetition, stereotpy, echolalia, perseveration till mutism supervenes	
Memory failures are variable	
Striatal signs of akinesia, rigidity emerge	
Frontotemporal dementia with motor neurone disease	
Anatomy	
Frontal chiefly orbito-frontal	
Temporal lobes (relative sparing of hippocampus, amygdale and thalamus)	
Histopathology	
Macrovacuolation, gliosis? Spongiform, fibrous astrocytosis, neuronal cell loss,	
Ballooned neurons	

Information sources: Neary et al. [65, 73], Nagaratnam and Nagaratnam [66], and Ash et al. [68]

subgroup of the patients with predominant striatio-temporal pathology, striatal signs of rigidity and akinesia develop early and are associated with stereotyped behaviour [73, 74]. Extrapyramidal disorder has occasionally occurred with FTD often with MND [73]. MND type inclusions have been found in FTD without clinical MND but there has been a significant number of cases of FTD and PPA developing clinical MND [54].

Diagnosis

Neuropsychological testing which evaluate language, memory, abstraction, visuospatial skills, planning and mental control, conduct and intelligence is useful to obtain a clinical appraisal of the disease. Executive functions (abstract types of tasks), impaired powers of abstraction, design competence and verbal response are affected rather than the visual and memory capabilities. Neuroimaging. Magnetic resonance imaging (MRI) is one of the most useful test to demonstrate the affected areas (frontal, anterior temporal lobes, left perisylvian cortex) in the brain depending on the different types of FTD.

Treatment

There is no cure. The mainstay of treatment is management of the behavioural symptoms.

Corticobasal Syndrome (CBD)

Introduction

CBD is characterised by hyperphosphorylated tau forming abnormal filamentous inclusions in the neurons and glia [7]. The incidence is 0.62 per 100,000 to 92 per 100,000 and the prevalence in the United States is 4.0–7.3 per 100,000 [75]. The mean age of onset is 63 years and the youngest 45 years [76]. Both CBD and Progressive supranuclear paralysis (PSP) show a similar pattern of tau expression but in CBD tau forms paired helical filaments [77]. Abnormality on chromosome may cause both diseases [78].

Clinical Manifestations

Corticobasal syndrome (CBS) with its constellation of features genetically, clinically and pathologically is similar to or overlaps FTD [79]. It presents with noticeable asymmetry a combination of cortical and extrapyramidal features [80]. A common presentation is the 'useless arm' (dystonic, rigidity, akinetic or apraxic) in more than half the cases [81]. Other presentations include a progressive disorder of language (progressive nonfluent aphasia, apraxia of speech [79] or praxis with typically asymmetric extrapyramidal abnormality and dystonia and parkinsonism are the most common features. Symptoms of apraxia, tremor, limb dystonia or cortical sensory disturbances and myoclonus are seen [82]. Supranuclear ophthalmoparesis and other abnormalities of eye movement and

myoclonus [80] are common. Apraxia of voluntary gaze resemble opthalmoplegia of PSP but with eye movements affected in all directions rather than solely the vertical and involuntary saccades are unaffected The patient often complain that the affected limb is not part of their body, a sensation called 'alien limb'. They often have cognitive difficulties and most commonly involve difficulty with expression of language such as word finding difficulty and naming. Similar to FTD they may exhibit frontal behavioural features [83] such as inappropriate behaviour, personality changes, repetitive and or compulsive activities (Box 4).

Box 4 Corticobasal Syndrome

Sixty year-old male with features of parkinsonism and cognitive function limb apraxia, rigidity, akinesia, alien hand.

Postural-action tremor/myoclonus,limb dystonia progressive gait difficulty supranuclear opthhalmoplegia cognitive profile-subcortical dementia

dd supranuclear paralysis, other cortical atrophies

Histopathology

Ballooned achromatic necrosis

Nigral and basal ganglia degeneration

Information sources: Mahapatra et al. [78], Rinne et al. [81], and Riley et al. [82].

Posterior Cortical Atrophy

Introduction

Posterior cortical atrophy is a progressive clinicoradiologic syndrome [84] characterised by an array of manifestations which include higher visual dysfunction and that of Balint's and Gerstmann's syndromes and transcortical sensory aphasia [85]. Is a rare disease and frequency is unknown [86]. PCA has been attributed to involvement of the parietal and occipital association cortices. Structural neuroimaging has demonstrated parieto-cortical atrophy and functional imaging has revealed bilateral hypometabolism and hypoperfusion [87]. It is unclear whether the changes in white matter integrity are due to ageing process or to some other pathology [88]. The syndrome is associated with a variety of underlying pathologies. The posterior cerebral areas show deposition of neuritic plaques and neurofibrillary tangles [86]. It is often defined as a variant or atypical form of Alzheimer's disease however the clinical presentation is distinctly differrnt from Alzheimer's disease. CT and MRI demonstrates bilateral parieto-cortical atrophy but no detectable mesiotemporal atrophy as seen in Alzheimer's disease [86]. Damage to the association cortices of the occipito-parietal regions which is associated with visuo-spatial integration produces disorders such as optic ataxia and simultanagnosia [89]. All the components need not be present to constitute the syndrome indicating that the syndrome does not depend upon a single brain mechanism [90].

Clinical Manifestations

There are several subsets in PCA consisting of variable number of components of the Balint's and Gerstmann's syndromes but the most common neuropsychological symptoms seen are that of full Balint's syndrome or some component of the syndrome [91]. Memory and cognition are spared till late in the course of the illness. Balint's syndrome is characterized by optic ataxia, apraxia of gaze and asimultagnosia. With time there is a progression of agnosia and apraxia which is disabling and with progression language and mremory become affected [86].

Dementia with Lewy Bodies (LBD)

Introduction

DLB also known as Cortical Lewy Body dementia or Diffuse Lewy-Body Dementia is a neurodegenerative disorder associated with abnormal

structures (Lewy Bodies) in certain parts of the brain. It is the second most common cause of dementia (15–20%) [8, 92] after Alzheimer's disease [8, 93]. DLB is characterized in most cases with neocortical or limbic Lewy bodies and Alzheimer type pathology below the threshold for the diagnosis of AD [94] but the cortical Lewy bodies and Lewy neuritis in DLB are the most important correlates of cognitive failure rather than the AD pathology [8]. The frequency and distribution of cortical Lewy Bodies has been defined by antiubiquitin immunocytochemical staining. It has been demonstrated that there is a link with 'synucleinopathies' which include Parkinson's disease and Multisystem atrophy [8] and classified as a alpha-synucleinopathy [92] and there is a marked cortical reduction of acetylcholine and nigrostriatal dopamine deficiency [93].

It could present like Alzheimer's disease or Parkinson's disease or a combination of the two [95]. The clinical symptoms suggestive of DLB are fluctuating cognitive impairment with episodic periods of confusion, visual hallucinations and extrapyramidal signs occurring either sponataneously [92, 93] or as part of an abnormal sensitivity to neuroleptic medication [96]. The survival time of patients with DLB is shorter than in AD. Depression and delusions are also frequent in DLB found in 60% of cases each [97] (Box 5).

Box 5 Lewy Body Dementia
Fluctuating cognitive impairment
Episodes of confusion
Visual hallucinations
Extrapyramidal signs
Sensitivity to neuroleptic medications
Repeated falls
Syncope
Anatomy: Lewy bodies-cortical and brain stem
Histopathological

Box 5 Lewy Body Dementia (continued)
Lewy bodies (spherical,intraneuronal, cytoplasmic
Eosiophilic inclusions

Information sources: Barber et al. [92], Arslan et al. [93], McKeith et al. [96], and McKeith et al. [98].

Diagnosis

It is clinically important to make an accurate diagnosis because of DLB's sensitivity to neuroleptic medications [92, 96]. The diagnosis is made on the presence of the above-mentioned core symptoms together with one of the following namely repeated falls syncope, neuroleptic sensitivity, hallucinations or delusions. The Consortium on Dementia with Lewy bodies [98] met to establish consensus guidelines for the clinical diagnosis of DLB. and for the characterization of pathological lesions at autopsy. The consensus criteria for the clinical diagnosis of probable and possible DLB includes progressive cognition decline, fluctuating periods of confusion,visual hallucinations, features of parkinsonism and supportive features such as repeated falls, syncope neuroleptic sensitivity, delusions and hallucinations [98]. Brain stem or cortical Lewy bodies are the only features considered essential for the pathological diagnosis of DLB [98]. Currently the most reliable biomarkers are the relative preservation of medial temporal volume on structural MRI and the use of SPECT tracers for regional blood flow [8].

Treatment

Cholinesterase inhibitors have been shown to be effective in improving cognition, neurological and psychiatric symptoms [8, 92, 93]. Some patients with DLB develop severe sensitivity

reactions with the atypical antipsychotics but are less likely to occur with the newer atypical antipsychotics [92].

Parkinsonism and Dementia

Parkinson's disease primarirly occurs after the age of 50, carrying the 7–10% of dementia in this age category [99, 100]. Dementia with parkinsonism poses difficulties in diagnosis. For instance parkinsonian motor deficits encroach on the diagnostic criteria for dementia by limiting activities or increasing dependency [101]. There are three phases of dementia in Parkinson's disease namely (1) that of Alzheimer' disease (2) that of cortical Lewy bodies and (3) cell loss in the nucleus basalis and remaining cells showing tangles [101]. A subgroup of PD with onset in late life demonstrates neuropathological changes of the Alzheimer's variety [102]. The prevalence rates of dementia in Parkinson's disease is said to be between 30% and 40%, a better estimate would be 20% [103]. but this is again doubtful [104]. Depression is much more frequently seen. Clinical and neuropathological similarities to AD are seen in 10–30% of Parkinson's disease patient (Box 6).

Box 6 Key Points: Neurodegenerative Dementias

Alzheimer's disease (AD) is a disorder of the amyloid precursor protein (APP) [5–8].

The fronto-temporal (FTD) syndromes and some of the extrapyramidal dementias (corticobasal, progressive supranuclear palsy) are associated with the micro-tubule-associated protein tau [5–8].

Other degenerative diseases including Parkinson's disease, multiple system disease and Lewy body dementia are associated with alpha-synuclein [5–8].

Five to 10% of patients with AD are familial with an autosomal dominant inheritance pattern.

Box 6 Key Points: Neurodegenerative Dementias (continued)

AD patients usually present with gradual progressive memory loss together with other domains of cognitive impairment.

FTD/Pick complex now refers to a group of disease which include Pick's disease, Fronto-temoporal Lobar Degeneration (FTLD).

Primary Progressive Aphasia (PPA), Semantic Dementia and be considered as Fronto-Temporal Dementia a part of Pick's complex [54].

Lewy body dementia (LBD) is the second most common cause of dementia (15–20%) after Alzheimer's disease [8, 92].

Vascular Cognitive Impairment (Major or Mild Vascular Neurocognitive Disorder)

Introduction

It has been suggested that VaD should be re-defined with greater consideration to the identification of distinct vascular mechanisms in the development of dementia [105] Currently the term vascular cognitive impairment (VCI) has been proposed [106]. It includes a wide spectrum of cognitive decline ranging from mild deficits in one or more cognitive domains referred to as Vascular mild cognitive impairment (VaMCI) to a broad dementia- like syndrome [107] including vascular cognitive impairment with no dementia and mixed Alzheimer's disease and cerebrovascular disease [108]. The Canadian Study on Health and Aging restricted the definition excluding cases of dementia. Vascular cognitive impairment without dementia was the most prevalent form of VCI among the 65–84 years old in the study [109]. The study further found that about half of the elderly with mild cognitive problems converted to dementia after 5 years [110]. It is a preferred term for it

encompasses the complex interactions between vascular risk factors, cerebrovascular disease etiology and cellular changes within the brain and cognition [111]. The term vascular cognitive disorder had been proposed by Sachdev [112] for cognitive impairment of vascular origin ranging fron VCI to VaD and includes such entities as mixed AD/CVD, poststroke VaD, poststroke VCI and Biswanger disease [106]. Vascular risk factors for VCI include diabetes, dyslipidaemia, obesity and metabolic syndrome [112].

VaD has been related to multi-infarct dementia, subcortical ischaemic vascular disease and dementia or small vessel disease [111], strategic infarct type dementias, subcortical arterioscleostic leucoencephalopathy (Binswanger), multilacunar stae and mixed cortico-subcortical type [113]. Vascular dementia is second most common cause of and in some countries it is the commonest [114]. The incidence of VaD is about 3.8% per thousand per annum and its incidence increases with age, in both men and women from 1.3 in those aged 65–69 years to 9.3 in those aged 85 years or over and to 15.9 in men over the age of 90 [115]. Subcortical VCI accounts for over 40% of all VCI [115].

Mixed VaD and AD

AD type lesions, cerebrovascular lesions and other pathologies coexist giving rise to mixed pathologies in 25–80% of the demented elderly [107]. Gorelick [116] considered the risks factors as 'putative' or 'tentative' for the reason there has been no general consensus about the risk factors for VaD and the likely explanation for this are the studies of different populations using disparate methods. The potential risk factors being demographic, atherogenic, genetic and stroke related factors [116]. Silent cerebral infarcts that are strategically placed in the deep frontal lobe and thalamus may prove significant in the pathogenesis of dementia associated with stroke [116]. Although the prevalence ranges from 12.9% [117] to 38% [118] the true prevalence in the general population is not known. Vascular lesions involving the frontal lobe may mimic AD with frontal involvement and the frontal variant of frontotemporal dementia (FTD). AD patients usually present with cognitive rather than social breakdown as well as personality change. In FTD the latter occur early with close similarities to the vascular frontal syndromes. However the onset is insidious with degenerative dementias and is progressive [119] (Box 7).

Box 7 Mechanisms of Vascular Dementia and Vascular Cognitive Impairment

I. Multi-infarct dementia
   (a) Cortical,subcortical, mixed
   (b) Lacunar
II. Single strategically placed infarcts
   (a) Angular gyrus syndrome (inferior parietal lobule)
   (b) Thalamic dementia (paramedian thalamic)
   (c) Caudate, gobus pallidus, basal forebrain, hippocampus
III. White matter ischaemia

Information sources: Jellinger 2013, 2004

Diagnosis

The accuracy of diagnosis of VaD is found wanting because of limitations of assessment scales available. Most criteria used in the diagnosis of dementia emphasize memory impairment [120] which is not a common finding in cognitive impairment with VaD. Several groups have proposed criteria for its diagnosis [121] but these criteria have been proposed for different purposes. Wetterling et al. [122] compared the different diagnostic criteria for VaD and discussed their limitations. The Hachinski Ischaemic scale is used in the diagnosis of VaD although it it more widely used for research purposes. Furthermore it has poor interrater reliability, is based on the

concept that VaD is caused by multi-infarction and does not include neuro-imaging [120]. The DSM-IV criteria published by the American Psychiatric Association [123] has not been validated. The International Classification of Disease (ICD-10) produced by the World Health Organisation (1993) [124] is subclassified into multi-infarction dementia, subcortical vascular dementia, vascular dementia of acute onset and mixed forms or unspecified types. The National Instuitute of Neurological Disorders and Stroke and expert panel (NINDS-AIREN) [125] used for a diagnosis of probable VaD requires the presence of (a) dementia (b) cerebrovascular disease and (c) a relation between the two (such as onset of dementia within 3 months of a stroke) (Fig. 1). The NINDS-AIREN and the criteria for the diagnosis proposed by the State of California Alzheimer's Disease Diagnostic and Treament Centers [121] incorporate neuroimaging technology, comprehensive neuropsychological parameters and brain necropsy findings to help to elucidate vascular mechanisms that may cause cognitive impairment. These criteria has been criticised for being over inclusive and overlapping and have not been validated [126].

A high percentage of patients become demented following a stroke and about two-thirds are said to be aphasic [126]. The type of aphasia will depend on the location of the lesion. The true incidence in this category is not known, since most studies have excluded patients with severe aphasia because of the difficulties in testing them adequately [126]. The presence of dementia was assessed by using the functional criterion [126]. Censori et al. [126] considered only those aphasic patients showing marked functional impairment that could not be explained by their communication deficits or hemiparesis. Jorm and Korten [127] studied the feasibility of measuring cognitive decline in the elderly directly from informants. They developed a standardized interview to measure decline in both intelligence and memory

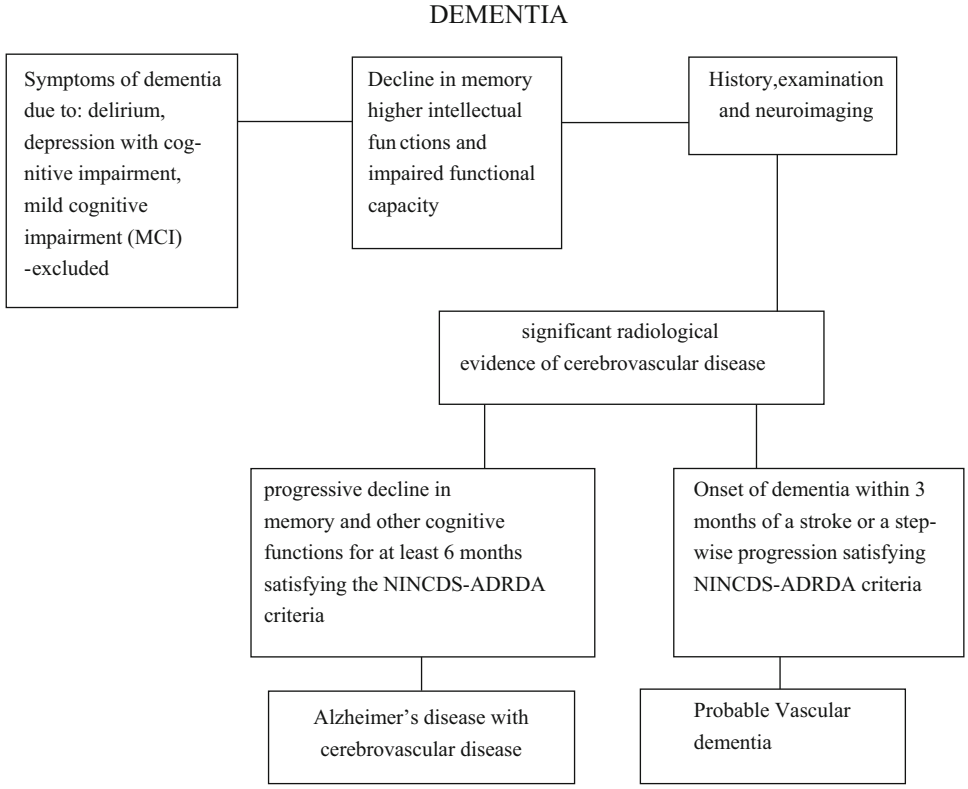

Fig. 1 Diagnosis of probable vascular dementia and mixed dementia (Alzheimer's with cerebrovascular disease)

of an elderly person's performance and 10 years earlier.They found this to be a valid measure of cognitive decline and had less contamination with pre-morbid ability than the MMSE. The use of informants had also been suggested by Henderson and Huppert [128] for the diagnosis of early dementia because they are better informed as to the parient's performance. Other workers found informant reports have little validity as to memory functioning in normal elderly. Until guidelines for a reliable criteria are established the clinician should assess the aphasic patient and suspect dementia in a global way and not just in one aspect of the patient's symptomatology [129].

Treatment

The risk factors should be looked for and modified. The risk factors are listed in Box 8. Deficits in neurotransmission and breakdown of neuronal circuits in the brain results in cognitive deficits whatever may be the type of dementia [130]. Cognitive deficits are associated with lowered nicotinic cholinerginergic neurotransmission and in the nembers of nicotinic receptors [130]. In investigating the effects of galantamine in patients with vascular dementia and mixed dementia it was shown that galantamine was effective on all key areas of cognitive and non-cognitive abilities in this group of patients [130] (Box 8).

Box 8 Risk Factors in Vascular Dementia and Treatment

(i) Hypertension, diabetes- antiplatelet -drugs
(ii) Atrial fibrillation-anticoagulantiii, carotid aryery disease- surgery
(iii) Vasculitis-steroids, Immunosuppressive drugs
(iv) Cerebral hypoperfusion – surgery
(v) Hereditary vascular dementia-genetic counselling

Information sources: Erkinjuntti and Gauthier [111]

Symptomatic Dementias

Creutzfeldt-Jakob Disease (CJD)

Introduction

A prion is an infectious protein particle capable of transmitting an infectious disease in both humans and animals. The prion diseases affecting humans are symptomatic dementias Creutzfeldt-Jakob Disease (CJD), Gerstmann-Straussler-Scheinker syndrome (GSS), Kuru, Fatal Familial insomnia (FFi) and Alpers Syndrome.

CJD is a rapidly progressive neurodegenerative disease with spongy degeneration of the brain and death within a year. It is rare affecting one person per million worldwide per year [131, 132]. There are about 200 cases per year in the United States [132]. The human disease may be inherited, acquired or sporadic forms. In a retrospective study, Bruton et al. [133] found that in only 60% of prion disease cases typical spongiform pathology was identified clinically during life suggesting that several cases are not detected. The agent associated with CJD is the prion protein (PrP) encoded by the gene on chromosome 20. This is converted via a conformational change to an abnormal protein PrPsc [134] and this accumulates as an abnormal protein designated PrPres which accounts for the degenerative changes in the cerebral cortex.

Clinical Manifestations

The clinical picture is diverse producing a number of different presentations. The age incidence ranges from 16 to 90 years with a median age 60–65 years [135]. Typically the first symptoms are personality changes with anxiety and depression [136, 137] with memory loss, difficulties in balance and coordination and jerky movements [243]. The classic CJD presents with a rapidly progressing [137] and myoclonus with other neurological and neurobehavioural signs such as pyramidal and extrapyramidal signs, cerebellar ataxia, visual disorders. Within 3–4 months there is usually a rapid decline to akinetic mutism. Pneumonia and other infections occur in these patients and can lead to death. Sporadic CJD is the most common but the mode of transmission is

not known [137]. There are six subtypes of sporadic CJD [138]. Iatrogenic or transmissible CJD occurs from certain medical procedures such as brain surgery, corneal transplants, grafts of dura mater, gonadothrophic hormone and from human growth hormone [139]. Familial CJD is characterised by may halotypes based on the PRNP mutation and condon 129 on the mutant allele [138]. It has an early onset around the age of 50. The variant CJD is associated with eating contaminated beef products and believed to be due to contaminated meat from cattle suffering from Bovine Spongiform Encephalopathy (BSE or "Mad Cow" disease) [137].

The EEG will depend on the stage of the disease. In the early stages diffuse slowing and frontal rhythmic delta activity and the late stages are characterised by periodic sharp wave complexes [140]. Histopathologically a triad of spongiform vaculoation, astrocytic proliferation and neuronal loss. Laboratory tests and findings: analysis of 14-3-3 abnormal protein in the cerebrospinal fluid by immunoassay [141] (this protein may be found in stroke and viral encephalitis), and immunoperoxidase staining of cells of lymphoid tissue (tonsil). An accurate clinical history, meticulous examination with use of the EEG, MRI and CSF protein tests provides a early diagnosis of CJD with increasing assurance [142]. The definite diagnosis can be made only when the neuropathology, immunocytochemical and prion western blots are positive [131] (Box 9).

Box 9 Key Points: Symptomatic Dementias-Creutzfeld-Jakob Disease

CJD is rare affecting one person per million worldwide per year [131, 132].

The age incidence ranges from 16 to 90 years with a median age 60–65 years [135].

Typically the first symptoms are personality changes with anxiety and depression [136, 137] with memory loss, difficulties in balance and coordination [137] and jerky movements [136, 137].

The EEG will depend on the stage of the disease. In the early stages diffuse slowing and frontal rhythmic delta activity and the late stages are characterised by periodic sharp wave complexes [140].

Histopathologically a triad of spongiform vaculoation, astrocytic proliferation and neuronal loss.

Laboratory tests and findings: Analysis of 14-3-3 abnormal protein in the cerebrospinal fluid by immunoassay [141].

AIDS Dementia Complex

One of the neurological complications of primary HIV-1 infection is AIDS dementia complex (ADC). Furthermore it is characterized by cognitive, motor [143] behavioural [144, 145] and mood changes in adults. It has been estimated that one in four newly diagnosed HIV infections occurs in older adults (2–4). About 11% of new infections occur in the 50 years and older and it is estimated that in the future more than half will be 50 years or older [146]. Age is an important factor in HIV related cognitive deficits and causes significant morbidity and mortality and accelerating the aging process [147]. In individuals under the age of 50 years it is the most treatable cause of neurocognitive impairment [143, 144]. It develops in advanced AIDS and may develop in 10–70% of patients with AIDS. Over the past few years the incidence of HIV associated dementia has decreased due to the highly active retroviral therapy but the neurological complications such as cognitive deficits persist (HAART) [143, 144]. The neurological damage in HIV/AIDS is not completely prevented by HAART [145] and persist [147]. Following the availability of HAART treatment it was found that only 2% patients with AIDS developed ADC. HIV involves typically the subcortical regions [147] and leads to cognitive and motor disorders [143, 144]. Cognitive impairment is characterized by memory loss, difficulty in concentrating and speech problems. Motor impairments are characterised by weakness of legs with difficulty in

walking, spasticity, loss of bladder control and behavioural by irritability, depression.withdrawal, psychosis and mania [148].

Diagnosis by mental status examination, examination of the cerebrospinal fluid and neuroimaging (CT, MRI and SPECT scans) [144] Neuroimaging studies had revealed global atrophy and SPECT showed patchy cortical and subcortical hypoperfusion [149]. The median survival after diagnosis of ADC is about 6 months before the use of AZT.

Normal Pressure Hydrocephalus (NPH)

The incidence and prevalence of NPH are increasing [150]. The prevalence of NPH in institutionalized patients may be upto 14% [151] and the overall prevalence increases with age [152] The incidence has been estimated as 1.8 per 100,000 [153]. Initially it was considered to be idiopathic [154, 155] but now by common usage includes any form of chronic communicating hydrocephalus [156]. The idiopathic form tends to present in the elderly [157] whereas the communicating in younger indiviuals [158]. There may be a precedent history of meningitis, subarachnoid haemorrhage, neurosurgery or head injury [158]. In most instances such a history is lacking.

A number of changes have been noted as possible links with NPH. The pathophysiology of NPH has been attributed to a number factors both mechanical [159] and ischaemic [160, 161]. Ventricular dilatation which occurs in NPH is most noted physiological change [162]. It has been suggested that the ventricular enlargement follows the damage to the deep white matter due to vascular disease associated with ischaemia [163] resulting in tissue loss [162]. It can also be due to close down of the arterioles in the deep white matter due to aging. Currently there is general acceptance of a close association between NPH and a global reduction in cerebral blood flow (CBF) [162] and it has been interpreted that the CBF reduction in NPH is secondary to ventricular dilatation [164]. There is a rise in the sagittal sinus pressure, the pressure gradient required to reabsorb CSF is exceeded and CSF absorption through the granulations ceases [165]. It has been suggested that the ventricular enlargement is due to transient high pressure hydrocephalus and with further enlargement the pressure returns to normal [166]. On the other hand others believe that the initial event is diminished CSF absorption in the arachnoid villi [166]. Slow absorption of the CSF, ventricular dilatation and frontal lobe abnormalities may result from a scarring of the arachnoid villi over convexities of the frontal lobes. Ischaemia in the deep venous territory is not a prerequisite for NPH [162]. Severe damage to the frontal lobes gives rise to clinical features very similar to that of normal pressure hydrcephalus which in effect a frontal lobe syndrome consequent to periodically raised intraventricular pressure [167].

The syndrome of normal pressure hydrocephalus is characterized by the classical triad of gait disturbances, progressive mental deterioration and urinary difficulties [154, 168]. As the disease progresses unsteadiness leads to falls, apathy, lack of spontaneity and depressive symptoms [169]. Psychiatric and behavioural symptoms characterized by agitation, paranoidal delusions, visual hallucinations and belligerence occuir in association with NPH [170, 171].

The diagnosis, however has been fraught with difficulties. There is no need for the triad to present in its entirety. The symptoms are common in the elderly. The gait abnormality appears first and most experts believe that gait impairment is a must for the diagnosis. The diagnosis of NPH is essentially a clinical one based on the symptoms followed by neuroimaging (CT or MRI) and both showing enlargement of the ventricles accurately [152]. In the elderly the enlarged ventricles are sometimes difficult to distinguish from normal aging. A RHISA scan may show changes of the circulation reflux of cerebrospinal fluid into the ventricles. Other bed side tests include that for memory,the Bingley memory test [172], and the Miller Fisher test which is a walking test before and after removal of approximately 30 ml of spinal fluid and is a good predictor of successful treatment with ventriculoperitoneal shunt [173]. It has been shown that the ventricular tap test is useful in selecting patients who will respond to

shunting as it has shown greater sensitivity and specificity [157]. The treatment is surgical, the results of treatment with cerebrospinal fluid shunting is inconsistent. Box 10 summarises the key points (Box 10).

Box 10 Key Points: Normal Pressure Hydrocephalus (NPH)

There may be precedent history of meningitis, subarachnoid haemorrhage or head injury [158].

It was considered to be idiopathic [154, 155] but now by common usage includes any form of chronic communicating hydrocephalus [156].

Ventricular dilatation occurs and is the most noted physiological change [162].

There is a close association between NPH and a global reduction of cerebral blood flow (CBF) and is said to be secondary to ventricular dilatation [162].

When the sagittal sinus pressure increases the pressure gradient required to reabsorb CSF is exceeded and C SF absorption ceases [165].

Others believe that the initial event is diminished CSF absorption in the arachnoid villi [166].

Severe damage to the frontal lobes gives rise to clinical features similar to NPH [167].

The ventricular tap test is useful in selecting patients who will respond to shunting as it has shown greater sensitivity and specificity [157].

Spirochaetal Infection

Lyme disease is caused by the spirochaete organism *Borrelia burgdorferi* which remains latent for several months to years and then manifest as a neuropsychiatric syndrome with CNS infection. Untreated Lyme disease can cause damage to the brain and cause dementia. The diagnosis is made by serology.

Traumatic Brain Injury

Traumatic brain injury (TBI) is a significant global problem in elderly patients [174, 175] and is a crucial public health and socio-economic problem world wide [175, 176]. It is a common in the elderly and adults 75 years and older and have the highest rates of TBI-related hospitalisation and death [174, 177]. It is responsible for more than 80,000 emergency department visits each year [174, 177]. The main cause is falls followed by motor vehicle accidents [175, 176]. The elderly with TBI have a poor outcome compared to younger elderly (aged 65–75 years [175]. Although several prognostic factors such as preadmission functional ability, comorbidities, gender and other factors have been identified, these variables have been understudied in the elderly with TBI [174]. Alcohol abuse, polypharmacy, drug interaction and elder abuse are some of the issues that require special attention [177].

The patients with TBI exhibit a variety of symptoms such as deficits in attention, memory, emotion, motivation and drive and inability to recognise the effects of one's behaviour [178]. Neurobehavioural sequelae are common following TBI and consist of a spectrum of somatic amd neuropsychiatric symptoms which are cognitive and behavioural [179].

The Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5) contains the diagnostic criteria for Neurocognitive Disorder (NCD) for TBI which require the presence of at least one of four features: loss of consciousness, post traumatic amnesia, disorientation and confusion or neurological sigs such as seizure, anosmia, visual field defects, hemiparesis or neuroimaging findings [180]. The NCD should have its onset immediately after the TBI or come on after recovery of consciousness and persist past the acute postinjury period [180].

Impact

Dementia is recognised as one of the most common devastating disease causing immense pressure on the health care system and families.

Among older people dementia is one of the most striking cause of disability and dependance. The age standardised prevalence of dementia has been estimated to vary from 5% to 7% of the world's population aged 65 years and older [181]. With the aging of the population an increasing number of older patients are diagnosed with dementia. The oldest old aged 90 years and older are the fastest growing segment and the highest rates of dementia in the population [182]. The prevalence rates increases with age doubling every 5 years [181]. The 2010 World Alzheimer Report highlights the economic impact of dementia worldwide and cost of illness studies have been carried out in the high income countries [183] In the United Kingdom the total population prevalence is 7.1% and equals 1 in every 14 of the population the over 65 s and the total cost will be UK 26 billion pounds a year [184]. There will be as many as 16 million Americans with Alzheimer's disease by 2050 an will cost all payers $20 trillion over the next 40 years [185]. In 2011 unpaid care provided by 15.2 million family members and friends is valued at over $210 billion [185]. In Australia therewill be over half a million by 203 and by 2050 it will be 1 million and the cost of care was estimted at $5.4 billion and the cost of replacing family carers with paid carers was estimated at $5.5 billion per annum in 2008 [186]. Presently 500,000 Canadians suffer from dementia and in a generation this will increase to 1,100,000 and the economic burden is $15 billion and this will increase within a generation to $153 billion [187] Dementia has a far reaching and intense impact not only on the dementia patient's life but also on the lives of the spouse, families and friends. A person recently diagnosed as having dementia may experience an array of symptoms such as anger, shock, disbelief, fear and grief. Spouses or daughters who are caregivers for older adults with dementia and living in community care settings caregiving can be most agonizing [188] and are often confronted with physical, social, emotional and financial problems. The welfare of the people with dementia is associated with the quality of their relationship with their informal carers [189] and a healthy relationship will ensure the person has a good quality of life.

Multiple Choice Questions

1. The following are true of Lewy body dementia (LBD), EXCEPT
   A. Fluctuating periods of confusion
   B. Presence of stroke disease
   C. Recurrent visual hallucinations
   D. Particularly sensitive to neuroleptics
   E. Repeated falls
2. The following are true of Fronto-temporal dementia (FTD), EXCEPT
   A. Personality changes
   B. Early loss of insight
   C. Progressive non-fluent aphasia
   D. Family history of 50%
   E. Gross memory impairment
3. The following are suggestive of Cortico-basal syndrome, EXCEPT
   A. Postural-action tremor
   B. Progressive gait difficulty
   C. Alien hand
   D. Vertical gaze palsy
   E. Memory spared
4. The following are suggestive of Vascular dementia (VaD), EXCEPT
   A. Focal neurological signs
   B. Stepwise deterioration
   C. Normal scan
   D. Abrupt onset
   E. History of strokes

MCQ Answers

1 = B; 2 = E; 3 = D; 4 = C

Extended Matching Questions

A. Lewy body dementia
B. Alcoholic dementia
C. Huntington's disease dementia
D. Normal pressure hydrocephalus
E. Parkinsonism and dementia
F. Alzheimer's disease
G. Vascular dementia
H. HIV dementia complex
I. Cruezfeldt-Jacob
J. Fronto-temporal dementia

The following patirents have in common dementia. Chose the diagnosis from the list above. Each option can be used only once.

1. A 65 year old man presented with fluctating cognitive impairment with episodes of confusion, visual hallucinations and extrapyramidal signs. He admitted to frequent falls and syncopal attacks.
2. A 68-year old woman was seen in the memory clinic with progressive memory loss. She has become forgetful over the past 12× months often asking the same questions several times in the day. Her quality of domestic chores is beginning to decline so has her personal hygiene.
3. A 55 year old man was seen with changes in his behavior. He exhibited childish behavior clowing joking and lacked concern over personal appearance. Furthermore he had undressed and urinated in public. He consumed large amounts of Soft drinks daily.
4. A 65 year-old man presented with difficulty in walking, urinary difficulties and forgetfulness. He demonstrated apathy, lack of spontaneity and depressive symptoms.

EMQ Answers

1 = A; 2 = D; 3 = J; 4 = G

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Behavioural and Psychological Symptoms of Dementia (BSPD) and Management

69

Contents

Abstract

The behavioural and psychological symptoms in dementia (BSPD) could be intrinsic to the disorder or occur across multiple diagnoses, for example, in primary psychiatric illness, chronic alcoholism, cerebral disorder (cerebral infarction), cerebrovascular disease, cerebral tumour and normal pressure hydrocephalus. The relationship between dementia and dementia-related behaviours remains unclear. There is a marked variation in their occurrence. Neurotransmitter abnormalities have been associated with behavioural symptoms. Most behavioural disturbances are possibly associated with the degree of dementia. Dementing disorders are accompanied by dangerous, disruptive, distressing and disturbing behaviours. BPSD consists of many symptoms, and they often occur in symptom clusters and recognized as subsyndromes or subsyndromal clusters. This review provides an overview of the behavioural and psychological symptoms of dementia and their clinical management.

Keywords

Behavioural and psychological symptoms in dementia · Neurotransmitter abnormalities · Subsyndromes or subsyndromal clusters · Cholinesterase inhibitors · Antipsychotics

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_68

Introduction

Behavioural disorders and psychiatric symptoms such as delusions, hallucinations and depression form an intrinsic part of the dementia syndrome. More than 100 behaviours have been described, and they are so varied that the definition of some could be debated. Behavioural disorders in the present context mean an abnormality of behavioural emotions or relationship that is inappropriate and of such severity and duration as to cause continued suffering, hardship or distress to the family and community [1]. In 1996, a consensus group consisting of 60 experts produced a statement that the term behavioural disturbances should be replaced by the term behavioural and psychological symptoms of dementia (BPSD) and defined as symptoms of disturbed perception, thought content, mood or behaviour that frequently occur in patients with dementia [2].

The relationship between dementia and dementia-related behaviours remains unclear. There is a marked variation in their occurrence. Swearer et al. [3] reported it to be 83% in Alzheimer's disease patients when seen over a period of 6–18 months, and in another study, 58% of the dementia patients had one or more disturbed behaviours [4]. Others have recorded lower incidence. This variation amongst other reasons could be due to the informants' perception of disturbed behaviour and in what part of the temporal course the patient was seen. Aggression or physical violence has shown a wide variation in its occurrence, ranging from 18% to 60% [5–8]. Wandering as a problem was seen in 70% of patients [6, 9, 10]. A study of 90 patients with dementia in the community revealed, 59% had aggression, 27% were wandering and 22% had delusions [4].The prevalence rate of incontinence varied from 21% to 40% [4, 5, 11].The incidence of vocalization and noisemaking in the hospital setting ranges between 26% and 44% [12] and 25% in nursing homes [13].

Neurotransmitter abnormalities have been associated with behavioural symptoms. The neurogenic pathways that control mood and behaviour are associated with neurotransmitters such as serotonin, dopamine and acetylcholine which have a modulatory role. Serotonin has been associated with disturbed behaviours [14]. The frontal lobe is closely associated with human behaviour. Hyperactivity, disinhibition, impulsiveness and distractibility are characteristic behaviours associated with orbitofrontal lesions. The frontal lobe and frontal subcortical circuitry play an important role in the occurrence of aggression and agitation [15] and have been linked to dysfunction of the serotogenic transmission. Agitation in Alzheimer's disease is a manifestation of frontal lobe dysfunction [15]. Delusional syndromes are known to involve the temporal lobe especially the medial limbic structures [16]. Behavioural overactivity was correlated with lower acetyl transferase activity in the frontal and temporal cortex in autopsy studies [17], and the frontal lobes of those with agitation had the greatest burden of neurofibrillary tangles in a study of histopathology in AD patients [18]. According to Cummings [19], the occurrence of different psychological syndromes could be influenced by several factors including genetic constitution [20], age of onset, personality characteristics [22, 21], early-life experiences and location and extent of lesions. Environmental provocators might also precipitate behaviour by evoking aggressive responses in patients whose threshold for agitation is affected.

The behavioural and psychological symptoms in dementia could be intrinsic to the disorder or occur across multiple diagnoses, for example, in primary psychiatric illness, chronic alcoholism, cerebral disorder (cerebral infarction) [23], cerebrovascular disease [4], cerebral tumour [24] and normal pressure hydrocephalus. It is important to identify and minimize and avoid stressors (for instance, physical stressors such as pain or any other medical illness), identify precipitants such as medications and possible drug interactions and identify activity-related behaviours and environmental factors such as restricting opportunity for choice amongst others.

Most behavioural disturbances are possibly associated with the degree of dementia [3, 6], and cognitive impairment was significantly correlated with agitation, apathy and aberrant motor behaviour [25]. Delusions, hallucinations and paranoia increased with cognitive decline [26, 27],

but others had found no difference across the three levels of severity of dementia. Mild to severe depression had been reported in 30–40% of dementia patients [28]. Amongst the individual symptoms, there are subtypes, some needing treatment, others do not, as, for instance, amongst the vocalizers, there are a spectrum of subtypes.

Classification

Behaviours form a wide spectrum. There have been several classifications set up for some types of behaviours such as for aggressive behaviours [29], wandering [30] and vocalization [31], but the last did not include some types of vocalization such as screaming, singing, talking and complaining [32]. Noisemaking behaviour was categorized into four subtypes based on the predominant character of the noise, namely, (1) persistent screaming; (2) perseverative vocalization; (3) continuous chattering, muttering, singing or humming; and (4) swearing, grunting and bizarre noisemaking [33].

Behavioural disturbances such as screaming, verbal outbursts, agitation, verbal and physical aggression and wandering have been proposed as a continuation of hyperactive behaviour. Symptoms often occur as symptom clusters or subsyndromes. Hope et al. [34] identified three syndromes: (1) overactivity (walking more, walking aimlessly, trailing the carer), (2) aggressive behaviour (physical aggression, aggressive resistance, verbal aggression) and (3) psychosis (anxiety, persecutory ideas, hallucinations). Amongst the patients with vocalization four symptom clusters emerge, namely, (1) screaming with verbal aggression, (2) screaming with motor restlessness, (3) screaming with psychotic symptoms and (4) screaming with depressive symptoms [35].

Clinical Manifestations

In 1907 Alois Alzheimer in his landmark case report described a 52-year-old woman with a disorder which continues to bear his name, who apart from having increasing impairment of memory and disorientation exhibited useless and purposeless behaviour characterized by dragging her bedding and objects around. She screamed for no reason and often screamed that her doctor wants to cut her up. She greeted her doctor as a visitor. She had auditory hallucinations and paranoid delusions and was suspicious of her husband and had delusions of sexual abuse. Thus there was a panoply of screaming, paranoid delusions, hallucinations, memory impairment, disorientation and bizarre behaviour in Alzheimer's disease [36].

Dementing disorders are accompanied by dangerous, disruptive, distressing and disturbing behaviours. They form a wide spectrum, and the frequently occurring ones include aggression and agitation, delusions (simple persecutory, complex persecutory, grandiose and those associated with specific neurological deficits) [19] and motor restlessness. The less frequent problematic are pathological stealing (shoplifting and pilfering), scatolia and altered eating habits (increased or decreased eating, binge eating) [24].

Management

BPSD consists of many symptoms, and they often occur in symptom clusters and recognized as subsyndromes or subsyndromal clusters. The well-recognized ones are those with verbal and physical aggression and motor restlessness – wandering and pacing, vocalizations, depressive symptoms and psychiatric symptoms. Analysis of the subsyndromes where several symptoms may coexist often reveals one or two behaviours which stand out as to severity and could be designated as the target symptom.

It is important to know the type of dementia for the pharmacological agents may behave differently in different dementias. The Lewy body dementia group poses challenges since neuroleptic medication can provoke severe, irreversible and often fatal sensitivity reactions [37]. The cholinergic enhancers have been proven to be effective in Alzheimer's disease and in Lewy body dementia but not so in the frontotemporal dementia where it is less likely to be effective and may in fact worsen.

Non-pharmacological

There are two different strategies available, the non-pharmacological with its multifaceted approach which is the mainstay of treatment and the pharmacological used as an adjunct intervention. There are other adjunct approaches such as using bright light, aromatherapy, white noise therapy and music, but none have been evaluated using group method methodology. However a double-blind controlled trial demonstrated that aromatherapy was safe and effective treatment for dementia-related agitation [38].

Pharmacological

There is an evidence-based approach to pharmacotherapy. The key issues are (1) to recognize the specific subsyndromal cluster; (2) to identify the target symptom; (3) to select the drug class, for some should be favoured for initiation in certain subsyndromes because there may be evidence of benefit on coexisting conditions; and (4) to select the individual drug in the drug class, and this is largely influenced by the known efficacy and the side effect profile of the drug which are largely based on RCTs or individual choices. However selecting an appropriate agent for treatment can be difficult.

Cholinesterase Inhibitors

Cholinesterase inhibitors are generally prescribed in Alzheimer's disease but have also been found to be effective in reducing agitation [39]. Delusions, depressed mood, sleep disturbance and auditory hallucinations are common neuropsychiatric features of Lewy body dementia. Neocortical activity as assessed by choline acetyl transferase is more severely depleted in LBD as compared to Alzheimer's disease [40], and there are extensive deficits in cholinergic transmission [41]. Hence cholinesterase inhibitors could be a more rational choice for LBD patients than neuroleptics [41, 42]. It is also postulated that cholinergic agents may have psychotropic activity through actions in the paralimbic cortex of the frontal and temporal lobes [43]. In a large double-blind placebo-controlled trial in moderate to severe dementia patients, donepezil improved the behavioural symptoms at the end of 24 weeks. The symptoms were aberrant motor behaviour (53%), depression/dysphoria (52%), agitation/aggression (45%) and apathy/indifference (67%). However, more evidence for this use is needed, and responses thus far have been variable [44].

Anticonvulsants

Valproic acid has been used in a number of case series and appears to be useful in practice and is generally well tolerated. The side effects are hepatotoxicity, ataxia and oversedation. The proposed mechanism of action is via the alteration of the gamma-aminobutyric acid (GABA) system and not the serotonergic system [45]. The use of carbamazepine in BPSD was positive in a study of its efficacy for agitation and aggression in dementia. Carbamazepine and valproic acid are increasingly used for BPSD particularly in patients with cerebrovascular disease and dementia [46]. A non-significant reduction in agitation was observed in 56 nursing home patients with valproate (median dose 826 mg/day) assessed against placebo [47].

Antipsychotics

Noradrenergic and serotonergic depletion are thought to contribute to behavioural symptoms [48], and antipsychotic agents are widely used for the management of behavioural symptoms. The typical antipsychotics like haloperidol are commonly prescribed but have a high extrapyramidal symptoms (EPS), hypotension, sedation and anticholinergic effect especially in the elderly complicated by age and comorbidity as compared to the younger adult [48]. More recently it has been shown that the conventional antipsychotics like haloperidol, thioridazine and

others were only marginally effective than the placebo [49]. In Lewy body dementia, antipsychotics can give rise to disastrous medical consequences such as tardive dyskinesia and possibly sudden death [50]. Furthermore there is evidence that antipsychotics have inhibitory effects on cholinergic, dopaminergic and histaminergic neurotransmission and thus give rise to deleterious cognitive effects in some older patients [51].

The newer atypical antipsychotics such as risperidone, clozapine, olanzapine and quetiapine manipulate the serotonin system [52] and are used for treatment of BPSD. They are a heterogeneous group of drugs that may be associated with lower risk of EPS and are better tolerated. Several studies have shown that risperidone is effective for treatment of agitation, aggression and psychosis and there was no significant cognitive decline in risperidone-treated elderly patients in two placebo-controlled trials [53, 54]. Increasingly international consensus is to use atypical antipsychotics for BPSD. The four studied antipsychotics, are risperidone, clozapine, olanzapine and quetiapine, and they appear to be relatively equivalent but have some differences in side effect profile. Clozapine although showed therapeutic benefits has high incidence of adverse effects such as sedation, seizures, postural hypotension, anticholinergic events and agranulocytosis [55].

Antidepressants

Depressive symptoms are common in dementia, but their cause remains unclear. Depression can lead to aggressive behaviours, and there is strong evidence for the value of selected antidepressants on managing patients with AD and depression. Sertraline has been found to be superior to placebo in reducing depression in patients with comorbid AD [56]. Selective serotonin reuptake inhibitors (SSRI) are better tolerated in older adults than the more traditional tricyclic antidepressants or monoamine oxidase inhibitors. Citalopram has been shown to be effective for depression and behavioural disturbance in dementia [57, 58]. Trazodone, a triazolopyridine derivative, inhibits the neural response of serotonin [59] and has been used in continuous and repetitive screaming patients with effect [60, 61]. Fluoxetine should be avoided in those with agitation and anxiety (Fig. 1 and Box 1).

Box 1 Key Points: BSPD

The term behavioural disturbances has been replaced by the term behavioural and psychological symptoms of dementia (BSPD).

The behavioural and psychological symptoms in dementia could be intrinsic to the disorder or occur across multiple diagnoses, for example, in primary psychiatric illness, chronic alcoholism, cerebral disorder (cerebral infarction) [23], cerebrovascular disease [4], cerebral tumour [24] and normal pressure hydrocephalus.

There is a panoply of behavioural and psychological symptoms in Alzheimer's disease.

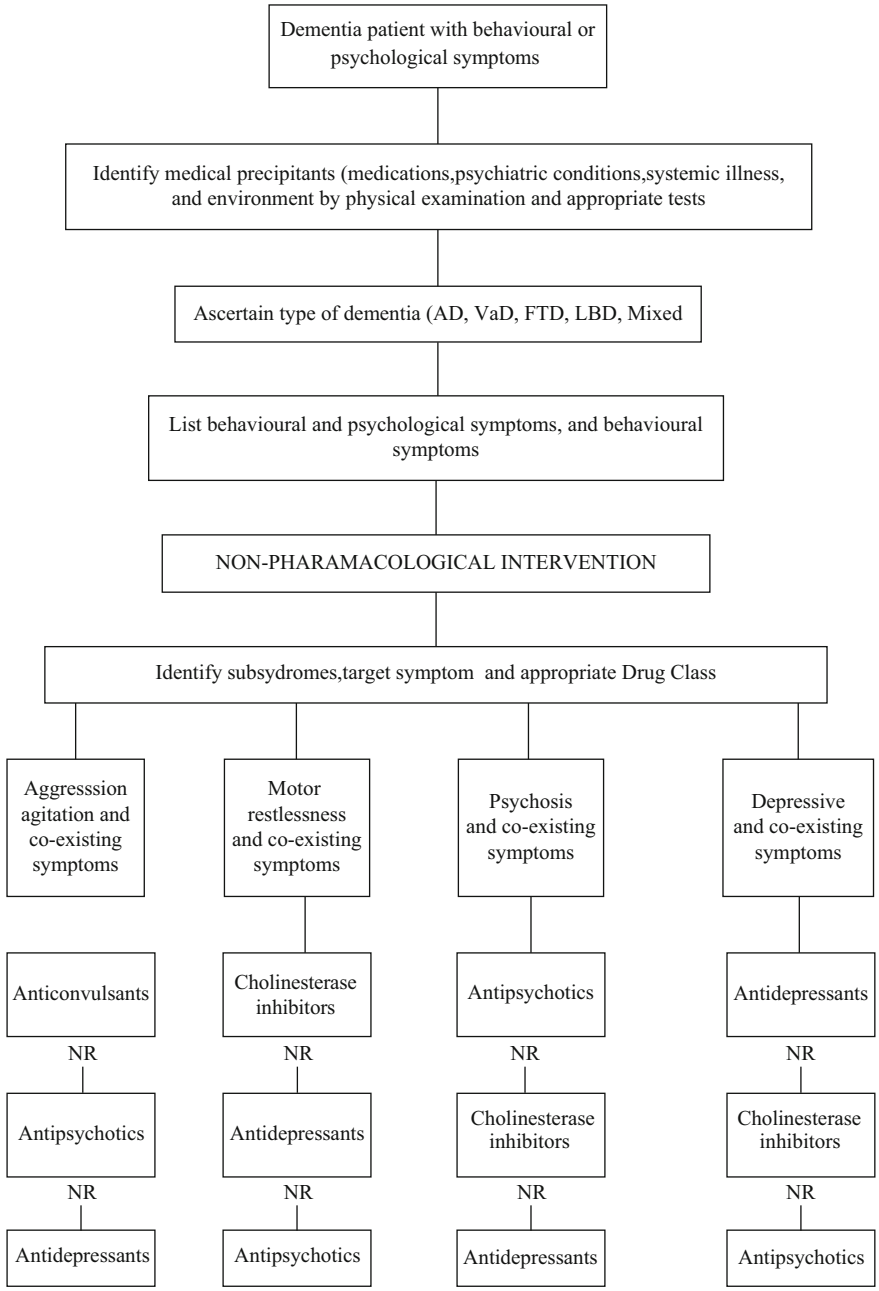
BPSD often occurs in symptom clusters and recognized as subsyndromes or subsyndromal clusters.

Hope et al. [34] identified three syndromes: (1) overactivity (walking more, walking aimlessly, trailing the carer), (2) aggressive behaviour (physical aggression, aggressive resistance, verbal aggression) and (3) psychosis (anxiety, persecutory ideas, hallucinations). Amongst the patients with vocalization, four symptom clusters emerge, namely, (1) screaming with verbal aggression, (2) screaming with motor restlessness, (3) screaming with psychotic symptoms and (4) screaming with depressive symptoms [35].

Where several symptoms occur in subsyndromes often reveals one or two behaviours that stand out and could be designated as target symptom.

Management: non-pharmacological and pharmacological.

(*continued*)



NR= No Response

** AD =Alzheimer's Disease; VaD= Vascular Dementia;FTD= Frontotemporal Dementia; LBD=Lewy Body Dementia

Preferred Drug Class and Individual drugs in the subsyndromes:Anticonvulsants: sodium valproate/carbamazepine;Antidepressants: SSRI-citaloprtam/sertraline;Antipsychotics: risperidpne/olanzapine;Cholinesterase inhibitors: donezepil/rivastigmine/gal

Fig. 1 Management of behavioural and psychological symptoms of dementia (BPSD)

Box 1 Key Points: BSPD (continued)

It is important to (i) recognize the specific subsyndromal cluster, (ii) identify the target symptom, (iii) select the appropriate drug class and (iv) select the individual drug.

Drug classes include (i) cholinesterase inhibitors, (ii) anticonvulsants, (iii) antipsychotics and (iv) antidepressants.

Selecting the individual drug in the drug class is largely influenced by known efficacy and side effect profile.

Impact

Dementia patients are susceptible to develop behavioural and psychological symptoms of dementia that can be difficult to address. BPSD is distressing to both patient and caregiver [62], influences the performance in daily life of the patient, adds to the burden and embarrassment experienced by the caregiver and the frustrations encountered by the treating physician and is a decisive factor for institutionalization [62, 63]. Behavioural disturbances often cause cognitive deterioration and accelerate admission to long-term care facilities [64]. It diminishes quality of life of patients and their caregivers [65, 66]. These disturbances often manifest acutely necessitating a physician's intervention. The primary care physician is often the first and most consulted professional and so most helpful in this direction. BSPD increases morbidity and increases cost of care [67].

Multiple Choice Questions

1. The following are true of behavioural and psychological symptoms of dementia (BPSD), except:
   A. BPSD often occurs in symptom clusters and recognized as subsyndromes or subsyndromal clusters.
   B. Behavioural disturbances often cause cognitive deterioration.
   C. Environmental provocators might also precipitate behaviour by evoking aggressive responses in patients.
   D. Acetyl Choline esterase inhibitors which are generally prescribed in Alzheimer's disease are not effective in reducing agitation.

MCQ Answers

1 = D

Case Study: Wandering and Its Prevention/ Management

Presentation. A 70-year-old man living with his wife had a 2-year history of memory and cognitive decline and a diagnosis of dementia of the Alzheimer type. He was a wanderer, wandering within the house and out of the house, and on several occasions had been lost and brought back by the police. His wife reported a horrendous story where her husband walked from the subway platform at the railway station on to the track and kept walking. Fortunately there were no tragic consequences. Curiously he still had a fair level of functioning but lacked insight and judgement. Subsequently he developed hallucinations and delusions.

Wandering is a common problem in dementia especially with Alzheimer's disease and can cause considerable risk to the patient as in the case presented. In the prevention and management, it is important to identify the cause. Some of the causes are shown in (Fig. 2). To prevent wandering it is necessary to determine the pattern of any and remove any triggers such as pain, physical discomfort and any other causes. Some of the measures in the management include someone to remain in the patients company, place visual barriers across the doors, regularly exercise and make the environment comfortable. Physical restraints have no place in the management.

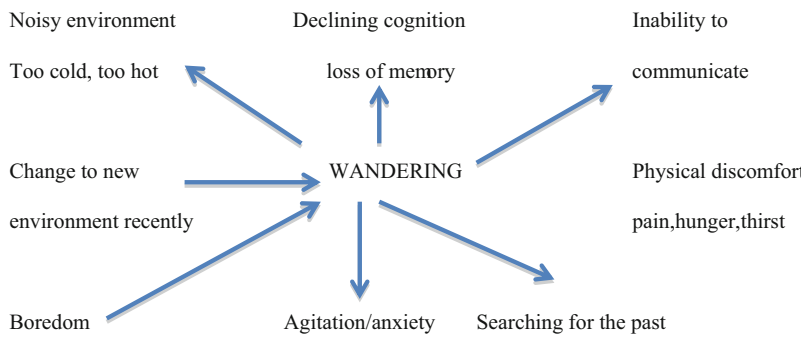


Fig. 2 Showing some causes for wandering (Information sources: Wandering. http://www.fightdementia.org.au/national/support=and-services/carers/behaviour-changes/wandering; Wandering behaviour. Bendigo Health. http://www.dementiamanagementstrategy.com/Pages/ABC_of_beha. . ..r_management/Management_strategies/Wandering_behaviour.aspx accessed 6 October 2016)

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Drug Management of the Dementias

70

Contents

Abstract

Recent increase in our knowledge and understanding of the pathophysiological mechanisms in AD has led to the identification of potential molecular therapeutic targets for the development of specific drugs. To date these new therapeutic approaches are directed on pharmaceutical compounds undergoing randomised controlled trials. The only successful treatment approach to date that has resulted in significant symptomatic benefit has been the cholinesterase inhibition, which prolongs central acetylcholine activity. Two types of cholinesterases are found in the brain – acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). There is evidence that AChE and BuChE have roles in the regulation of ACh levels. The three choline esterase inhibitors are the foremost treatment options for mild to moderate stages of dementia. Randomised clinical trials have shown consistent but modest benefits in all three outcomes. The present review will summarise the min group of cholinesterases with the main focus on their effects and adverse effects.

Keywords

Neurodegenerative diseases · Alzheimer's disease · Cholinesterase inhibitors · Acetylcholinesterase · Butyrylcholinesterase · NMDA antagonist

Introduction

Alzheimer's disease is a progressive neurodegenerative disease that is characterised by alteration in memory, visuospatial ability, abstraction and language together with deterioration in activities in daily living. Behavioural and psychological symptoms are commonplace but are often underscored [1]. Alzheimer's disease is characterised by marked cerebral atrophy and the presence of neurofibrillary tangles and neuritic plaques in areas of the brain such as the cerebral cortex, the amygdale and the hippocampus. It is one of the commonest forms of dementia in old age. There is a progressive decline in patients' ability to carry out first the more complex and subsequently even the basal activities of daily living. Once these are lost, they are rarely recovered. Whilst the aetiology is

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_67

unclear, several factors have been postulated to contribute to the development of the disease; amongst those with strong correlation are age, familial factors, Down's syndrome and apolipoprotein E e4 gene allele [2].

Recent increase in our knowledge and understanding of the pathophysiological mechanisms in AD has led to the identification of potential molecular therapeutic targets for the development of specific drugs [3]. These compounds are divided into anti-amyloid agents that block or inhibit overproduction of Abeta peptide or facilitate its clearance and those that target other pathological pathways [3]. Systemic injection of Abeta peptide based on active immunisation with the actual Abeta peptide [4] prevented the deposition of Abeta peptide. A clinical trial had to be discontinued because a significant proportion of the patients developed meningoencephalitis [5, 6]. To date these new therapeutic approaches are directed on pharmaceutical compounds undergoing randomised controlled trials [3].

Several mechanisms have been suggested for the disease process, but the one that is accepted is a widespread cholinergic deficit associated with loss of cholinergic transmission which is said to underlie the symptomatology [7–9]. The cholinergic deficit correlates closely both with the severity of the disease and the pathological changes [10].The cholinergic dysfunction has a central role that results in cognitive deficits especially memory in Alzheimer's disease. This is supported by several findings such as the degeneration of the cholinergic neurones [11], reduced number of cholinergic receptors and decreased activity of the enzyme (choline acetyl transferase) necessary for the synthesis of acetylcholine [7].

The only successful treatment approach to date that has resulted in significant symptomatic benefit has been the cholinesterase inhibition, which prolongs central acetylcholine activity. Hence the enhancement of the cholinergic function would be the most successful strategy to improve memory and other cognitive deficits [12]. Cholinergic function could be enhanced by three main mechanisms: firstly to increase the synthesis of acetylcholine (ACh) by the use of ACh precursors such as lecithin, secondly by stimulating the cholinergic receptors and thirdly by inhibition of the enzyme acetylcholine esterase (AChE), the enzyme responsible for the breakdown of ACh. Increasing the synthesis of ACh has not proved successful. The last two approaches have shown promise, that is, increasing the concentration of ACh available for the synaptic transmission and using AChE inhibitors and stimulating nicotinic and muscarine receptors with agonists. Nicotine agonists can increase ACh levels through stimulation of presynaptic nAChR which controls the release of A-Ch. Synaptic transmission can be increased or decreased by a chemical mediator by a process called modulation [13]. In 'positive allosteric modulation', the modulator binds to the same receptor as the one used by the natural agonist but uses a different binding site to the one used by the natural agonist (described as allosteric, meaning 'other site') [14], and one of the most potent allosteric modulator is galantamine.

Two types of cholinesterases are found in the brain – acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). There is evidence that AChE and BuChE have roles in the regulation of ACh levels and may play a role in the development and progression of AD. AChE is mainly located in the neurons and responsible for four fifths of the ChE activity, whereas BuChE which occurs in the glial cells accounts for the remaining one fifth [15]. It appears that the alterations to the ratio of AChE to BuChE are reduced to two thirds of normal levels in advanced AD in specific areas of the brain while BuChE activity increases [16]. Specific BuChE inhibitors and use of the ChE inhibitors with the ability to inhibit BuChE in addition to AChE should lead to improved clinical outcomes [17]. Rivastigmine is an inhibitor of both AChE and BuChE.

Drug Category

Cholinesterase Inhibitors

Donepezil: Donepezil is a reversible AChE-selective inhibitor of the piperidine chemical class and has a long half-life of approximately 70 h [18]. Significant cognitive benefits in patients

with mild to moderate AD have been demonstrated [19], although the effects on activities of daily living and behaviour have been more modest [20, 21]. It is contraindicated in sick sinus syndrome or other supraventricular conduction abnormalities, seizures and asthma. Its side effects include hallucinations, nightmares and vivid dreams.

Rivastigmine: Rivastigmine is a second-generation carbamate slowly reversible ChEI with a half-life of 7 h [18]. It is a centrally selective dual ChE inhibitor, targeting both AChE and BuChE with brain regional specificity for the hippocampus and cerebral cortex. It has produced significant effects on cognition and activities of daily living in mild and moderate AD [22, 23] and improved BPSD in mild to moderate AD [24, 25] (Table 1).

Galantamine: Galantamine is a tertiary alkaloid selective for AChE but not for butyrylcholinesterase. It also interacts allosterically with nicotine acetylcholine receptors to enhance the action of agonists at these receptor sites. Its half-life is 5 h [18]. It is well tolerated and is effective in the short term (up to 6 months) in patients with mild to moderate AD improving cognition and function. It delays the development of BPSD [26]. In the long term (up to a year), it maintains cognition and activities of daily living. Most frequent adverse events are nausea, vomiting, diarrhoea, anorexia and weight loss. It can cause bladder flow obstruction and potentiate tendency to seizures. The benefit of ChEI in the treatment of AD should be assessed on a regular basis and discontinuation considered if therapeutic benefit is no longer demonstrable.

The three choline esterase inhibitors are the foremost treatment options for mild to moderate stages of dementia [27] (Table 2). Randomised clinical trials have shown consistent but modest benefits in all three outcomes [28]. All three

Table 1 Drug category – cholinesterase inhibitors and NMDA antagonist

Drug category	Donepezil	Rivastigmine	Galantamine	Memantine
Chemical structure	Piperidine	Carbamate	Tertiary alkaloid	Structure
Mode of action	AChE inhibitor	AChE and BuChE inhibitors	AChE and nicotine receptor	NMDA receptor antagonist
Start dose	5 mg daily	1.5 mg bid	4 mg bid	5 mg
Maximum dose	10 mg	6 mg bid	12 mg bid	10 mg bd
	With meals	With meals		
	Morning	(Capsule or	(Tablet)	Tablet
		(Tablet)	Liquid	Liquid
Titration	10 mg in 4 week intervals	4 weekly intervals	4 weekly	
Contraindications	Hypersensitivity sick sinus, supraventricular conduction defects	Hypersensitivity	Hypersensitivity	History of seizures
Side effects	GIT effects	GIT effects	GIT effects	Fainting
	Nightmares	Sleep disorder	Weight loss	Confusion
	Vivid dreams	Diarrhoea	Tendency to seizures	Chest discomfort
	Hallucinations			

Table 2 Drug management of dementias

1.Alzheimer's disease	2. Lewy body dementia	3.Vascular dementia	4. Mixed dementia	5. Frontotemporal dementia
ChEI beneficial	ChEI beneficial	ChEI beneficial	ChEI beneficial	ChEI harmful
++	+	+	–	–
Consider to treat with cholinesterase inhibitor(ChEI) (1–4)				

cholinesterase inhibitors cause gastrointestinal side effects such as nausea, vomiting, diarrhoea and loss of appetite. Sleep disorders occur in all three but less likely with rivastigmine and galantamine. The risk of gastrointestinal symptoms can be reduced when rivastigmine is taken with food.

NMDA Antagonist

Memantine: Degeneration of the neurones of the brain can be caused by too much stimulation by glutamate. The glutamate that is released attaches to the receptor on the surface of the cells' N-methyl-D-aspartate (NMDA), and it has been proposed that continued activation of NMDA receptors by glutamate can be a contributor to the pathogenesis of AD [28]. Memantine blocks the receptor and decreases the effects of glutamate. It is used in moderately severe dementia. Like the cholinesterases, it does not stop the progress of AD. It is available as tablets (5 mg and 10 mg) and as a solution. Side effects include fainting, confusion, chest discomfort, hallucinations and seizures amongst others. It is contraindicated in patients with renal impairment and a history of seizures [29, 30] (Box 1).

Box 1 Key Points: Drug Management of Dementias

- In Alzheimer's disease, several mechanisms have been suggested for the disease process, but one that is accepted is the widespread cholinergic deficit with loss of cholinergic transmission [7–9].
- The cholinergic dysfunction has a central role that results in cognitive deficits especially memory in Alzheimer's disease.
- The cholinesterase inhibitors (donepezil, rivastigmine and galantamine) prevent the breakdown of acetylcholine by blocking the enzyme acetylcholinesterase. They are treatment options for mild to moderate stages of dementia [27].

Box 1 Key Points: Drug Management of Dementias (continued)

- Memantine is used in moderately severe dementia.
- Donepezil is a selective reversible AChE inhibitor [18]. *Rivastigmine is a centrally selective dual ChE inhibitor that targets both AChE and BuChE.
- Galantamine is a selective inhibitor for AChE and interacts with nicotine acetylcholine receptors.
- Memantine is a NMDA receptor antagonist and prevents overstimulation in the CNS by glutamine.
- It is important for the primary care physician to know the mode of action of the cholinesterase inhibitors as to which one to treat with and when to treat.

Multiple Choice Questions

1. The following are true of medications used in dementia, EXCEPT:
   A. Memantine is used in moderately severe dementia.
   B. Rivastigmine is a centrally selective dual ChE inhibitor that targets both AChE and BuChE.
   C. Donepezil is a selective reversible AChE inhibitor.
   D. Galantamine is a NMDA receptor antagonist and prevents overstimulation in the CNS by glutamine.

MCQ Answers

1 = D

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Mild Cognitive Impairment (MCI)

71

Contents

Abstract

Currently it is accepted that the DSM-5 mild neurocognitive dementia (NCD) is derived from research on mild cognitive impairment (MCI). Several labels have been used to categorise non-disabling memory deficits in the elderly. Unlike age-associated memory decline (AAMI), MCI is assumed to have a pathological basis and is at high risk of developing dementia, more than half progressing to dementia within 5 years. MCI has now been expanded to include other cognitive domains and other potential causes like normal ageing, frontotemporal dementia and vascular dementia. Nonamnestic forms may be due to cerebrovascular disease, Parkinson's disease, Lewy body dementia and frontotemporal dementia amongst others.

Keywords

Mild neurocognitive dementia · Mild cognitive impairment · Age-associated memory decline · Nonamnestic forms · Amnestic forms

Introduction

The Diagnostic Statistical Manual-5 (DSM-5) published by the American Psychiatric Association distinguishes between 'major' and 'mild' neurocognitive disorders (NCD). The DSM-5 mild NCD is defined by using several cognitive and related criteria which refer to cognitive changes, functional activities and exclusion of delirium and competing mental disorders together with two specifiers, the presence or absence of behavioural problems and presumed aetiologies

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_66

of mild NCD [1]. Currently it is accepted that the mild NCD is derived from research on mild cognitive impairment (MCI) [2]. Although there is no common consensus in defining MCI, clinicians and researchers refer to MCI as a category with objective evidence of impairment on cognitive testing that do not meet the criteria for dementia [3]. It is believed to be an intermediate state between normal memory loss of ageing and conditions such as Alzheimer's disease [4, 5]. The incidence rates of predementia syndromes increase with age and are higher in individuals with less education [6]. The incidence rates range widely, and this is largely due to different criteria being used [5, 6]. The incidence rate of amnestic MCI subtype ranged from 9.9 to 40.6 per 1000 person years and that of nonamnestic from 28 to 36.3 per 1000 person years [7]. The prevalence rates ranged from 3% to 20% depending on the concept used, and the incidence rates varied from 8 to 77 per 1000 person years [8]. The age and sex standard incidence rate of MCI was 63.6 per 1000 person years, and it was higher for men than women [9]. The estimated occurrence rate of AAMI is 39% in the ages 50 and 59, increasing to 85% in the over 85 group [10].

Several labels have been used to categorise non-disabling memory deficits in the elderly [6]. These include age-associated memory impairment (AAMI), age-associated cognitive decline (AACD), mild cognitive disorder (MCD), age-related cognitive decline (ARCD) and mild cognitive impairment (MCI) amongst others and are within the limits of normal ageing. In spite of the deficits, they did not exhibit the characteristics of dementia. Clinicians and researchers till recently were unable to provide firm answers concerning the significance of these categories and what they mean for the future. Unlike AAMI, MCI is assumed to have a pathological basis and is at high risk of developing dementia, more than half progressing to dementia within 5 years [11]. The aetiology of MCI is multifactorial and includes neurodegenerative, vascular, neurological, psychiatric, traumatic and iatrogenic [12]. MCI has been classified into amnestic and nonamnestic forms [12, 13]. Memory impairment predominates in the former and is frequently a prodrome of Alzheimer's disease. In some cases, autopsy studies have demonstrated an increase in proteins forming amyloid plaques and neurofibrillary tangles. Whereas the nonamnestic form is characterised by a variety of cognitive impairments involving single or multiple cognitive domains, more recently, multiple subtypes of MCI had been proposed, namely, amnestic MCI with single domain, amnestic MCI with multiple domains, nonamnestic MCI with single domain and nonamnestic MCI with multiple domains [8, 12, 14], based on intention to indicate the heterogeneity in aetiology of different subtypes of dementia [15]. It is believed that each subtype is associated with an increased risk for a specific type of dementia [16]. MCI has now been expanded to include other cognitive domains and other potential causes like normal ageing, frontotemporal dementia and vascular dementia [17]. Nonamnestic forms may be due to cerebrovascular disease, Parkinson's disease, Lewy body dementia and frontotemporal dementia amongst others [13].

Clinical Manifestations

Patients with MCI commonly present with complaints of increasing forgetfulness, for instance, forgetting to keep appointments or social engagements, difficulty in finding words or at times difficulty in finding their way in familiar surroundings. They often have difficulty in following or focussing on conversations. The patient may exhibit anxiety or frustration. The exact number of individuals with MCI who develop AD varies. Different subtypes progress at different rates and vary widely amongst studies [6, 18], and patients with amnestic MCI are at higher risk of developing AD [12], and a substantial number of those with multiple or nonamnestic cognitive impairment may not progress to dementia [5]. The conversion rate to Alzheimer's disease was 56% for amnestic MCI, 50% for amnestic subthreshold MCI and 52% for nonamnestic MCI [19]. In other studies, it was 21.9% over a

period of 3 years [20] and 23–47% over 2.6 years [16], and the conversion from MCI to overt dementia is 10–15% per year, and the majority of which is Alzheimer's disease [21]. There are a number of variables that may influence conversion to dementia. Neuropsychiatric disorders are quite common with MCI and are an important risk of progression to dementia [2]. The occurrence of depressive symptoms leads to a faster cognitive decline [20, 22, 23]. In hospital-based studies, the prevalence of depression with MCI was 44.3% (median) and in the population-based studies 15.7% [20]. According to Panza et al. [23], depressive symptoms may be an early identifiable clinical stage of dementia rather than a risk factor. A higher age, lower education and hypertension were found to have a higher risk of incident MCI [7]. Worsening of executive functions and functional status was found to be independently associated with conversion to dementia but not worsening memory [24].

Differential Diagnosis

AAMI includes individuals who have a significant age-related memory loss that affects their daily life. It appears more frequently in individuals with affective disorders from low sociocultural levels both affecting their objective memory performance [25]. The symptoms are generally stable and do not progress towards a pathological decline characteristic of dementia [26]. Patients with depressive disorders may manifest anxiety and complain of inability to concentrate or poor memory.

Diagnosis

Petersen et al. [21] assigned the following diagnostic criteria to MCI, subjective complaint of memory loss, objective memory impairment and other cognitive functions being normal, with no functional loss. This proposition is the most widespread and validated subtype and had the highest predictive value for conversion to dementia [15]. In 2004, Petersen et al. [27] distinguished three subtypes with different categories of progress: (i) amnestic MCI which is said to progress to AD, (ii) MCI with slight impairment of multiple cognitive domains (some may progress to AD or may represent normal cognitive ageing process and also vascular dementia) and (iii) MCI with isolated cognitive domain other than memory and may progress to non-AD-type dementia.

Clinical history of memory complaints corroborated by family member

To rule out drug abuse, depression or other mental illness, delirium and others which may affect cognitive functions

Physical examination, laboratory tests and neuroimaging to exclude possible dementia

Cognitive testing: Mini-Mental State Examination

To identify objective memory:

Logical Memory Delayed Paragraph [28]

Immediate recollection results are recorded following reading of a paragraph, and recall is tested after 15 min delay.

Neuroimaging: A study of patients with MCI who had abnormal fluorodeoxyglucose positron emission tomography (FDG-PET) and episodic memory impairment, found that these patients were 11.7 times more likely to convert to AD than those with normal FDG-PET and normal episodic memory [29]. Whole brain and hippocampal volumes can predict progression of MCI to AD [30–32], and N-acetylaspartate/creatinine spectroscopy is a sensitive assessment for discriminating MCI from AD [33].

Treatment

There is at present no treatment available for MCI. Lifestyle changes should be encouraged. Population-based longitudinal epidemiological studies have shown that exercise and physical activity are associated with a lower risk of dementia. The role of cognitive stimulation is less firmly established.

Impact

The gait in older adults with mild cognitive impairment (MCI) may be affected in several ways. They have poorer balance control ability compared to healthy elderly subjects [34]. Under cognitive challenges, MCI appear to affect specific gait parameters and static balance [35]. The gait problems may appear long before symptoms of MCI occur [36]. Poor balance predicts falls [37], and it has been shown that the risk of falls is greater in MCI subjects compared to non-MCI subjects [38]. The poor balance has been associated with lower grey matter densities in the middle and superior frontal gyri in older adults with MCI [37]. Their capacity to process emotional facial expressions indicates that cognitive abilities modulate the processing of emotions [39]. Spatial navigation such as learning new routes and drawing a map may be affected in nonamnestic MCI patients for they performed poorly compared to elderly healthy subjects [40].These changes may have a significant impact on the patient's activities of daily living (Box 1).

Box 1 Key Points: Mild Cognitive Impairment

Several labels have been used to categorise non-disabling memory deficits in the elderly [6].

The aetiology of MCI is multifactorial and includes neurodegenerative, vascular, neurological, psychiatric, traumatic and iatrogenic [12].

MCI has been classified into amnestic and nonamnestic forms [12, 13].

More recently, multiple subtypes of MCI had been proposed, namely, amnestic MCI with single domain, amnestic MCI with multiple domains, nonamnestic MCI with single domain and nonamnestic MCI with multiple domains [8, 12, 14], based on intention to indicate the heterogeneity in aetiology of different subtypes of dementia [9].

The conversion rate to Alzheimer's disease was 56% for amnestic MCI, 50% for amnestic subthreshold MCI and 52% for nonamnestic MCI [19].

Worsening of executive functions and functional status was found to be independently associated with conversion to dementia but not worsening memory [24].

Petersen et al. [21] assigned the following diagnostic criteria to MCI, subjective complaint of memory loss, objective memory impairment and other cognitive functions being normal, with no functional loss.

Multiple Choice Questions

1. The following are true of mild cognitive impairment, EXCEPT:
   A. It is believed to be an intermediate state between normal memory loss of ageing and conditions such as Alzheimer's disease.
   B. Currently, MCI includes other cognitive domains and other potential causes like normal ageing, frontotemporal dementia and vascular dementia.
   C. The exact number of individuals with MCI who develop AD varies.
   D. MCI with isolated cognitive domain other than memory and may not progress to non-AD-type dementia.

MCQ Answers

1 = D

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Part XVI

Psychiatry of Older Adults

There is considerable evidence that mental illness is widely prevalent in the elderly. Depression among the elderly may be twice as common as dementia. The presence of personality disorders, neurosis, and alcoholism is probably no lower among the elderly than in the younger age groups. Although the psychiatric disorders of the elderly have some special features, they do not differ significantly from psychiatric disorders in younger adults. The older people however have some unique features that can confound the diagnosis. Part XVI provides information on mental issues that are common to the elderly.

Depression is the most common disorder in individuals 65 years and older. Late-onset depression develops as a result of complex interactions of risk factors such as age-associated neurobiological changes, stressful events, a higher interaction with cognitive decline, and impaired effect of genes. The "vascular hypothesis is upheld by comorbidity of depression, vascular risk factors, vascular disease, and the association with ischemic lesions to characteristic behavioral symptoms. More lately there has been considerable move toward embodying structural brain changes and cerebrovascular pathology in the frontal, subcortical, and medial temporal structures. Mania usually occurs as a phase of manic-depressive disorder, but it can occur in association with medical and pharmacological states. Anxiety disorders are common in later life and are as common as in the young. In about half the patients, the anxiety disorder comes for the first time in late life and in the other half is a persistence of what started in early life.

The more notable psychosis of late onset are delusional disorder, schizophrenia, and psychosis in patients with dementia or depression. This article will focus on delusional disorder and late-onset schizophrenia. Suicide rates increase progressively with age. The highest suicide rates occur among persons aged 65 years and older and is about 50% higher than in young people. Substance abuse in the elderly includes alcoholism, to a lesser degree illicit substances, prescription medications, and over-the-counter medications. An estimated 10% of all cases treated by geriatric mental health facilities are alcohol and substance abuse and together with mental health problems are concurrent and interactive.

Mood Disorders (Major Depression, Bipolar Disorder)

72

Contents

Abstract

Depression is the most common disorder in individuals 65 years and older. Late-onset depression develops as a result of complex interactions of risk factors such as age-associated neurobiological changes, stressful events, a higher interaction with cognitive decline and impaired effect of genes. The 'vascular hypothesis' is upheld by co-morbidity of depression, vascular risk factors, vascular disease and the association with ischaemic lesions to characteristic behavioural symptoms. More lately there has been considerable move towards embodying structural brain changes and cerebrovascular pathology in the frontal, subcortical and medial temporal structures. Mania usually occurs as a phase of manic-depressive disorder, but it can occur in association with medical and pharmacological states. This review will give an update on recent advances on the pathophysiology of mood disorders and their clinical management in the elderly.

Keywords

Depression · Late-onset depression · 'Vascular hypothesis' · Mania · Manic-depressive disorder

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_73

Introduction

Depression is characterised by significantly lowered mood with little or no interest or pleasure in activities that are usually gratifying. Depression is the most common disorder in individuals 65 years and older [1]. In a study of 74 outpatients with depression, 80% had their onset of depression after the age of 60 [2]. The prevalence of major depression is between 5% and 10% of the people seen in the primary care setting [3] and is around 5% in the general population [4]. About 3% of the general population are diagnosed by the primary care physician each year, and equal number may be unrecognised [5]. In a community-dwelling population, the prevalence rates had been reported between 6% and 20% [6, 7]. Two Australian studies found the prevalence of depression in 8.2% of 22,252 community-dwelling people [8] and 34% in aged care residents, respectively [9].

Approximately 5% of the patients who consult the primary physician show major depression, another 5% milder forms and a further 10% some depressive symptoms [10]. In older people depression is often associated with anxiety [11]. According to the Australian Bureau of Statistics [12], depression and anxiety affect one in seven (14%) and one in four (26%) people, respectively, at some part of their lives. Women are affected twice as often as men.

Primary depressive disorder has been divided into 'early-onset disorder' (EOD) and 'late-onset disorder' (LOD). Major depression depicts a new condition arising in about half of the patients in old age (late-onset depression), and half or less had their first experience of depression before old age (early-onset depression) [13]. The age used to cut off between EOD and LOD varies, in the United Kingdom [14] and Australia [15] it is 60 years, and in the United States it is 50 years [14]. Late-life depression develops as a result of complex interactions of risk factors such as age-associated neurobiological changes, stressful events [13], a higher interaction with cognitive decline and impaired effect of genes [13, 16]. A family history of depression is more likely with EOD than with LOD [17]. Table 1 shows the

Table 1 Differences and similarities between early- and late-onset depression

	Early-onset depression	Late-onset depression
Age at onset	<60 years	60 years or more
Gender	F > M	F = M
Risk factors		
Family history	Increased rate	Lower rate
Genetic susceptibility	Increased effect	Poorer impact
Stressors	Increased rate	Lower rate
Cognitive impairment	Lower rate	Greater rate
Dementia	Lower prevalence	Higher prevalence
Structural brain abnormalities		
Cortical, subcortical atrophy	+	+++
Hippocampal volume	Reduced	+++
Reduced prefrontal lobe volume		+++
Fronto-temporal dysfunction		+++
White matter hyperintensities		+++
Symptomatology		
Loss of interest	+	+
Suicidal thoughts	+	+
Anxiety	+	–
Somatic symptoms	Less common	Common
Cognitive impairment	+	++
Anhedonia	+	++
Executive dysfunction	–	++
Episodic memory dysfunction	–	++
Prognosis		Poorer outcome
Treatment		Slow or poor response to antidepressants

Information sources: Holroyd and Duryee [2]; Baldwin and O'Brien [14]; Brodaty et al. [15]; Hickie et al. [18]; Baldwin and Tomenson [19]; Rapp et al. [20]; Elderkin-Thomson et al. [21]; Bhalla et al. [22]; Sheline et al. [23]; Papazacharias et al. [24]

differences and similarities between early- and late-onset depression.

Clinical Presentations

Numerous physical and physiological changes occur in the ageing patient that can mimic symptoms of depression. Often common depressive symptoms are incorrectly attributed to old age or to poor health with the result depression in old age may be unrecognised or untreated for a long time. There are several factors in old age that may be associated with depression, for instance, lack of social support, retirement, deterioration in activities of daily living, declining health and immobilisation [25, 26, 27], and furthermore the elderly are increasingly exposed to stressful life events and personal losses [28]. The elderly have some unique features that can often confuse the diagnosis [1, 29]. In later life depression may be a risk factor for the expression of Alzheimer's disease, and depression may occur as a prodrome for Alzheimer's disease [30].

Depression in primary care practice differs considerably from those seen at the psychiatric outpatients in their clinical characteristics. They are less severely ill with fewer depressive symptoms and shorter illness. These features may influence the primary care physician's decision to treat with antidepressants [31]. Elderly patients with depression show a wide range of clinical presentations. They may exhibit typical symptoms or behavioural disturbances, psychomotor retardation, 'pseudodementia' [32], florid form and somatic symptoms [33] among others. Particularly relevant to the elderly with LOD are cognitive impairment, somatic symptoms, vascular disease and cerebral structural abnormalities [34].

The typical picture of moderately severe depression includes symptoms akin to that seen in younger patients [33]. They show markedly depressed mood with loss of interest in enjoyment, feeling of worthlessness or guilt, reduced confidence and self-esteem, disturbed sleep, reduced appetite and decreased libido. There is lack of energy with poor concentration, pessimistic views of the future and suicidal ideation.

The behavioural changes such as restlessness, general slowing down, behaving out of character and denial of depressive feelings among others may indicate underlying depressive disorder [35]. Patients living in aged care facilities or long-stay hospitals manifest behaviours such as refusal to eat, wilful starvation, screaming and persistent or intermittent problematic and inappropriate behaviours such as urinary and faecal incontinence and scatolia, apparent and wilful falls, belligerancy directed towards other residents and nursing staff, violent behaviour, biting and scratching, all on a background of mild cognitive impairment. If the risk is not recognised, it may be mistaken for dementia [36]. Apathy is a common presentation in late-life depression with overtly sad mood less common [37].

Another important controversial presentation is depressive pseudodementia. There is a close similarity of symptoms of depressive pseudodementia and true dementia that can make differentiation of these conditions difficult in their clinical courses [38, 39]. There are several clinical similarities between the two disorders, and depression is often accompanied by cognitive symptoms [32]. Thus patients with dementia have been erroneously diagnosed to have depression and vice versa [40].The term pseudodementia is often used to refer to apparent dementia in depressed patients or in patients with non-organic psychiatric disorders. Dementia has a number of causes, but an incorrect diagnosis of dementia as a cause depression in an elderly patient can be hazardous [41] for the deficit is at least partially reversible. In a long-term follow-up of depressive pseudodementia, 89% of the patients studied developed Alzheimer's disease [42]. There are also reports of pseudodementia being associated with organic brain disorders [43, 44]. The use of the term 'pseudodementia' can be misleading, for some may dismiss the possibilities that underlying dementia or other organic disorders are present [45].

Depression in older people is often masked by somatic symptoms [46]. Somatic depressive symptoms include weight loss, anorexia, fatigue, agitation, headache, chronic pain, sexual

dysfunction and sleep changes, and it can present with any somatic symptom. In the elderly hypochondriasis [47] is a recognised symptom of depression [36]. Psychotic symptoms [46], insomnia, hypochondriasis [47] and subjective memory complaints are morbid conditions, and physical disabilities are often associated with depression in older people [6]. Women at the onset of menopause complain of dry eyes. Box 1 shows some of the somatic symptoms.

Box 1 Somatic Symptoms

Palpitation
Dyspnoea
Dizziness
Numbness and tingling
Trembling
Dysphagia
Nausea
Sweating
Flushes
Chills

Screening

Depression is often underdiagnosed and undertreated. About half of the patients with mental disorders or depression are treated by the primary care physician. Less than half of the patients affected are accurately diagnosed [29]. The detection of depression is often impeded by patient's culture, gender or the predominance of somatic symptoms [48]. This is reflected as barriers found in self-reporting screening tools used to detect depression [48]. Furthermore patients' interpretation of its emotional terms and their cultural conception of depression may affect the reliability of the scales [48].

There is no lack of clinical scales to help in the recognition of depression. Some of the instruments are questionnaires, some are self-reported, and others are interviews, and there is considerable debate about which is better. The Hamilton Depression Rating Scale (HDRS) is an interview-administered rated measure. It requires trained healthcare official and takes about 20–30 min. There are 17 or 21 items. The first 17 contribute to the total score. The items 18–21 are not part of the scale but give more information about the depression, and this includes paranoid symptoms among others. There is an interviewer bias, and this can impact the results. The Hamilton Depression Rating Scale (HDRS) [49] which has a high dependence on somatic symptoms is useful and more sensitive than the Geriatric Depression Scale that focuses more on cognitive symptoms. Geriatric Depression Scale (GDS) [50] has long and short forms. It is the most widely used scale in the elderly. It is a self-reporting questionnaire with a simple yes/no format. The Becks Depression Inventory [51] consists of 21 items to be completed by the patient, and each item is rated on 0–3 scale. It is said to be not ideal for older patients. The Zung Self-Rating Depression Scale is also completed by the patient [52]. More recently a short screening tool for depression consisting of two questions with a 'help' question (TQWHQ) was found to have a sensitivity of 79% with the general practitioners and a specificity of 94%. The authors claim that patients are unlikely to receive unnecessary treatment [53].

Diagnosis

Primary care physicians may have difficulty in detecting and treating depression unless they have a high index of suspicion and additional mental health training [54]. It is not uncommon or unusual for someone to feel depressed which is normal. However distinguishing 'normal' depression from major depressive episode involves consideration of the severity, persistence and duration and the presence of characteristic symptoms. According to the DSM-IV criteria [55] (Box 2), the diagnosis of major depression requires the presence of five of the main symptoms including depressed mood and loss of pleasure in all activities. In DSM-5 [56] the diagnostic criteria for

major depression remain largely unchanged from that of DSM-IV with one exception in relating to bereavement. In DSM-5 the symptoms of depression in the context of bereavement qualify for the diagnosis of major depression, whereas in DSM-IV, in the diagnosis of depression the bereavement has to be present for more than 2 months.

Box 2 Diagnostic Symptoms for Major Depression (DSM-IV) [55]

1. Depressed mood
2. Anhedonia
3. Weight changes
4. Sleep disturbances
5. Psychomotor disturbances
6. Lack of energy
7. Excessive guilt
8. Poor concentration
9. Suicidal ideation

The diagnosis of depression is a clinical one, and what is most important is the ability to recognise depression. TQWHQ can be used to screen patients by asking two questions and adding an optional third question [57]. One positive reply should lead to asking about other core symptoms to confirm the diagnosis. High-risk groups include those with history of depression, a family history, multiple physical illnesses, neurological conditions, chronic pain, another psychiatric diagnosis, recent adverse life events and frequent uses of health services [58]. It is important to recognise the distinction between psychotic and nonpsychotic patients for the reason that the response rates to different treatments for each subtype are different in the two groups. The psychotic patients are older than the nonpsychotic and may appear demented with more marked psychiatric disturbances.

Once the diagnosis is known, the next important task in primary care is the assessment of risk. High risks of self-harm and harm to others in all ages are well known. Other risks to self include social isolation, neglect of self-care, substance abuse, neglect of other medical problems, poor compliance with medications and access to lethal means [58, 59]. A number of considerations precede treatment. The patient should undergo thorough psychiatric and medical assessment including a suicide assessment. The elderly before making serious suicide attempts frequently contact family and doctor [60]. Several studies have revealed that 70% of the elderly suicide victims saw their primary care physician within a month of death. LOD is associated with a greater incidence of completed suicide and poorer outcome [61].

The SAD PERSONS is a quick and useful risk assessment tool [62] and reviewed by Juhnke [63]. *S* sex, *A* age, *D* depression, *P* prior history, *E* ethanol abuse, *R* rational thinking loss, *S* support system loss, *O* organised plan, *N* no significant other, *S* sickness. Scoring system 1 points for each positive answer on the above. Score: 0–2, no real problems, keep watch; 3–4, send home, but check frequently; 5–6, consider hospitalisation involuntary or voluntary; 7–10, definitely hospitalise involuntarily or voluntarily. The most important variables in this scale are age (elderly or adolescent), alcohol dependence and a history of suicide attempts.

It is useful to categorise depressed patients who are potentially suicidal into three groups [64]: (i) patients with ideation, plan and intent, (ii) patients with ideation and plan but without intent and (iii) patients with ideation but no plan or intent. Figure 1 suggests an algorithm for screening, diagnosis, risk assessment and management.

Treatment

*R*isk assessment is followed by formulation of a management plan. The clinician must have an understanding of the pharmacokinetics which differ considerably with age and the pharmacokinetics of individual drugs. Compliance is a problem in the elderly particularly in those suffering from psychiatric illnesses [65], and one reason for this is the occurrence of adverse effects. Having

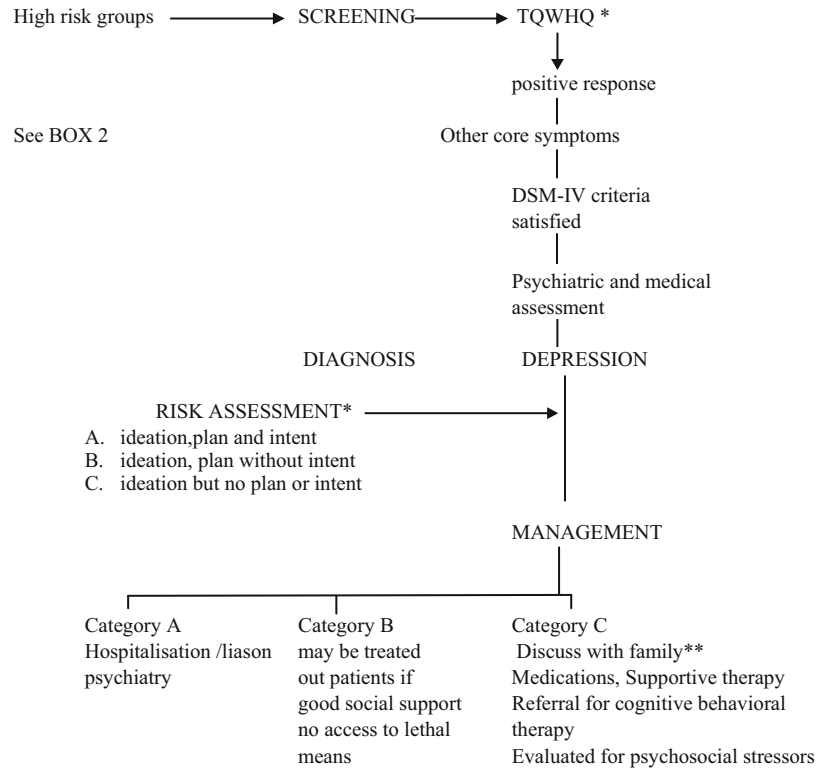

Fig. 1 Screening diagnosis risk assessment and management (* Information source: Frierson et al. [64])

* Information source: Frierson et al [64].

arrived at a diagnosis, it would be necessary to ascertain as to where to treat, in terms of immediate safety concerns and the factors to be considered for the need for hospitalisation which include an unclear diagnosis, drug and alcohol abuse, risk of harm to patient and others, lack of social supports (lives alone or too ill for self-care) and whether ECT is required.

The goals of treatment are listed in Box 3. There are several treatment options available for depression including medications, psychotherapy and electroconvulsive therapy or a combination in the more difficult cases. Pharmacological therapy remains a vital part of management, and treatment of depression is aimed primarily at full remission of the depressive symptoms. Non-pharmacological treatment includes electroconvulsive therapy, psychotherapy, cognitive and behavioural therapy, psychodynamic psychotherapy and life review therapy [66].

Box 3 Aims of Treatment

Recognition of the diagnosis
Remission of the depressive symptoms
Improve quality of life
Increase functional activities
Improve family and social relationships
Prevent relapse and recurrence
Find a job
Organise ones' home

Information sources: Battle et al. [67]; Treatment of depression [68]

Medical Therapy

Antidepressants

Antidepressants are central to the management of major depression in the elderly. In the treatment of major depression, studies have shown that

efficacy of antidepressants currently available is of equal value [65]. However the most important single factor in selecting an appropriate antidepressant for the elderly is the careful consideration of the likely side effect profile and potential reactions. Older patients experience adverse effects from antidepressants more frequently than younger patients.

SSRI is the first choice for treatment of depression among older patients [69] because of better safety and tolerability. They are safe and have fewer side effects, but there is greater risk of hyponatraemia in the elderly. The efficacy of SSRIs, MAO inhibitors and tricyclic antidepressants has been shown to be similar in randomised clinical trials [70]. There are possible drug interactions due to other medicines. Paroxetine and fluoxetine interact with cardiovascular drugs such as simvastatin, amlodipine, diltiazem, propranolol and metoprolol. Sertraline and citalopram have less potential for these interactions. Agitation and anxiety are commonly observed with fluoxetine and sertraline and sexual dysfunction with sertraline and paroxetine. Venlafaxine has a significantly higher side effect rate than sertraline in frail older patients [71] but may be balanced by superior efficacy [72]. A recent study in the United Kingdom of 60,746 patients between the ages of 65 and 100 years with new episode of depression found that SSRIs were associated with the highest adjusted hazard ratios for falls [73]. The tricyclics are generally not recommended in the elderly because of the anticholinergic and alpha-adrenergic blocking effects. Nortriptyline has the least potential for adverse effects.

SSRIs except fluoxetine are preferred first-line antidepressants for the elderly (Fig. 2). Paroxetine is associated with more anticholinergic side effects. Venlafaxine, mianserin, nefazodone and tricyclics have all been associated with blood pressure effects and may be an additional risk factor for falls. Where tricyclics are indicated, nortriptyline should be used as it has the least anticholinergic side effects. If there is no response after 4–6 weeks, switching to another drug is

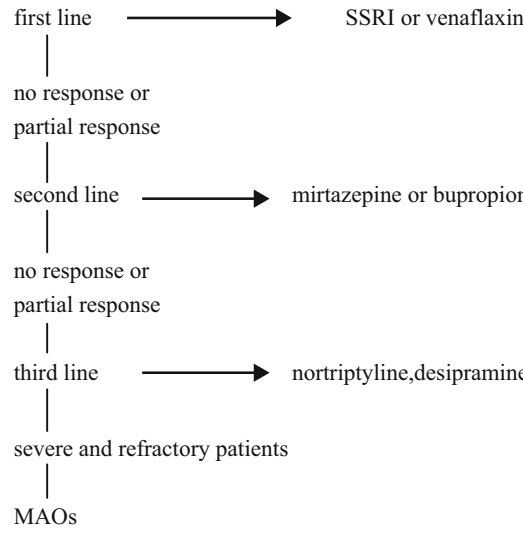

Fig. 2 Treatment of major depression of older patient

recommended. If there is partial response after 4–6 weeks, a further period or an increase in dose is justifiable. For major depression a 6–12 months or even longer course is advisable [74] and in those with recurrence a maintenance treatment up to 3–5 years, for instance, if there has been two or more major episodes within 5 years. A 'washout period' is usually required with antidepressants when switching from one to another with the dose halved at weekly intervals. The withdrawal has to be gradual with a drug-free period to avoid a serotonin syndrome (Box 4). Most reactions are mild and require no treatment, but severe cases can be treated symptomatically or the antidepressant reinstated before being gradually withdrawn [75]. Withdrawal symptoms are most with paroxetine and least with fluoxetine. In discontinuation symptoms a common feature

Box 4 Clinical Features of Serotonin

Confusion, hypomania, agitation
Sweating, fever, diarrhoea, shivering, elevated blood pressure
Tremors, myoclonus, incoordination, brisk reflexes

Table 2 Antidepressants for use in older patients

	Initial dose	Range	Adverse effects
I. Selective serotonin reuptake inhibitors (SSRI)			
Sertraline	25 mg	50–150 mg	Agitation
Fluoxetine	5 mg	5–60 mg	Agitation, insomnia
Paroxetine	5–10 mg	10–40 mg	Sexual dysfunction, anticholinergic effects
Citalopram	10 mg	20–40 mg	Few drug interactions
Escitalopram	5 mg	10–20 mg	Similar to citalopram
II. Bicyclic (SNRI)			
Venlafaxine	37.5 mg	75–225 mg	Discontinuation and blood pressure effects
III. Norepinephrine and dopamine reuptake inhibitors			
Bupropion SR	100 mg	100–150 mgbd	Agitation, insomnia, lowered seizure threshold
IV. Serotonin antagonist (NaSSA)			
Mirtazapine	5 mg*	30–45 mg	Weight gain, sedation
V. Tricyclics			
Secondary amines			
Desipramine	10–25 mg[a]	50–150 mg	Cardiovascular and anticholinergic effects
Nortriptyline	10–25 mg[a]	75–150 mg	Cardiovascular and anticholinergic effects
Tertiary amines			
Amitriptyline	25 mg[a]	150 mg	
Doxepin	25 mg[a]	150–200 mg	
Imipramine	25 mg[a]	150–200 mg	

Information source: Wiese et al. [77]
[a]At bedtime

which occurs within few days of stopping the antidepressant can cause significant morbidity and can be misdiagnosed leading to inappropriate treatment [75]. Venlafaxine has a significant discontinuation syndrome akin to SSRIs. A strategy to suppress the discontinuation symptoms is switching to fluoxetine [75].

The National Institutes of Health (NIH)-sponsored study, STAR*D, revealed that in monotherapy with SSRIs and SNRIs, the remission rate ranged approximately between 28% and 45% [65]. The results indicated that with the most commonly prescribed agents the benefit was seen only in less than half of the depressed patients. The trials also provided evidence for the use of rational combination pharmacotherapy in the treatment of major depression [76]. Independent of age of onset, depression has been shown to be associated with cognitive deficits [22] and may complicate treatment options [13]. Nevertheless depression in the presence of dementia should be treated for it is amenable to treatment [13]. Other antidepressants available include desvenlafaxine and duloxetine; both SNRIs and the latter have been shown to be effective treatment for depression in the elderly [77] (Table 2).

Electroconvulsive therapy (ECT) is an alternative treatment and is used more often for depression in older adults [78] and has been shown to be effective though adverse events such as cardiac complications, delirium and memory loss suggest prudence in its use in older adults [13]. Elderly patients with major depressive disorder treated with ECT and antidepressants showed good therapeutic response to both ECT and antidepressive therapy at the end of 1 year [79]. ECT is recommended as a first-line treatment of the elderly with psychotic depression [80] and is relatively safe and effective treatment for depression [77]. Transcranial magnetic stimulation (TMS) has shown moderate success in treating depression [81] (Box 5).

Box 5 Key Points: Depression

Primary depressive disorder is further divided into 'early onset ' and 'late onset' [13].

The LOD is closely linked to clinical and neuroimaging evidence of cerebrovascular disease [18].

The primary care physician should not rely solely on the results of the screening tools for the diagnosis of depression.

For the primary care physician two important symptoms alluding to depression are (i) persistent and pervasive depressed mood and (ii) loss of interest and motivation.

Elderly patients with depression show a wide range of clinical presentation.

High-risk groups include those with history of depression, a family history, multiple physical illnesses, neurological conditions, chronic pain, another psychiatric diagnosis, recent adverse life events and frequent uses of health services [58].

Primary care physicians need to be familiar with suicide risk assessment techniques.

Several options are available for treating depression including medications, psychotherapy and electroconvulsive therapy or a combination in more difficult cases [66].

In the treatment of major depression, studies have shown that efficacy of antidepressants currently available is of equal values [65].

Antidepressants are central to the management of depression in the elderly.

Electroconvulsive therapy (ECT) is an alternative treatment and is used more often for depression in older adults [78].

The primary care physician should liaise with others, e.g. family, mental health professionals and other family care practitioners, more actively in collaborative treatment of long-term risk reduction.

Dysthymic Disorder in Older Adults

Dysthymia is a chronic depressive disorder which is characterised in older adults by ideational symptoms of poor esteem, chronic pessimism and hopelessness [82]. It is not uncommon among depressed elderly outpatients [83]. The DSM-IV TR criteria require fewer diagnostic symptoms over a longer duration, at least over 2 years as compared with major depression [84]. It also notes one clinical characteristic – a distinction between early- vs late-onset dysthymic disorder [85]. Late-onset dysthymic disorder is typically different from early-onset dysthymic disorder [86] and is distinct from dysthymia in younger patients [83]. In older adults there is no gender difference, and it is associated with stressors or life losses and medical co-morbidities [87], and cerebrovascular disease has a role in its aetiology [86]. Older patients with dysthymia are at increased risk of suicide, but risk is less compared with major depression [88] and have been associated with feeling of guilt, sinfulness, worthlessness and pessimism [87]. DSM-5 has replaced 'dysthymia' with 'persistent depressive disorder', and this includes both dysthymic disorder and chronic major depressive disorder giving more emphasis to duration than to severity of symptoms [89] (Box 6).

Box 6 Key Points: Dysthymic Disorder

Late-onset dysthymic disorder is typically different from early-onset dysthymic disorder and is distinct from dysthymia in younger patients.

Mania in Old Age

Introduction

In bipolar disorders full-fledged mania and major depressive episodes alternate. In the depressive phase the symptoms are that seen in unipolar depression but for hypersomnia, psychomotor retardation and stupor at times which are distinc-

tive. Mania is characterised by elevation of mood, increased activity, and often with frank hostility; the speech is often rapid, and in the severe form of the disorder there is flight of ideas. Sleep is reduced, appetite is increased and so is sexual desire, but in older persons there is less sexual preoccupation. Apart from this age has little influence on the symptomatology between old and young [90]. Thought activities are expansive and may be accompanied by grandiose delusions. The patient, for example, is convinced that he is all powerful, a man of wealth, a leader or one who had an aristocratic ancestry. Auditory and visual hallucinations may occur (Box 7).

Box 7 Core Features of Mania

Elated mood
Aggression
Irritability and hostility
Decreased sleep
Impulsive behaviour
Over-talkativeness
Restlessness
Increased activities
Increased sexual activity
Poor attentiveness

There are three stages in the course of the manic disorder based on the severity: mild, moderate and severe. In the mild form there is increased physical activity; in the severe stage, in one with uncontrolled overactivity, thinking is muddled with delusions and hallucinations [91]. There is occasionally senseless agitation known as 'delirious mania' which is potentially life-threatening and under-recognised [92], or the patient is in a stupor and is mute and immobile, called 'manic stupor'.

Clinical Manifestations and Diagnosis

Bipolar disorder constitutes a spectrum of mood disorders, bipolar I, bipolar II, cyclothymic and other types, based on the severity and nature of the mood episodes. In bipolar I disorder there is current or the history of at least one manic episode lasting for more than 7 days and usually but not necessarily episodes of depression. Bipolar II is characterised by episodes of hypomania and depression. Hypomania has the same yardstick as mania but of shorter duration of at least 4 days and not severe enough to impair function significantly. Manic symptoms cover a spectrum of severity from a cyclothymic to severe delusional mania. In older adults late-onset bipolar disorder is possible but is not the most likely diagnosis [93]. A conscientious evaluation for any underlying neurologic disease especially cerebrovascular disease should be done in mania in old age [94] .

Treatment

i. Mood stabilisers such as lithium or divalproex sodium are viable treatment, but in older adults it may tend to have side effects [95]. The elderly have difficulty in tolerating lithium because of the neurological side effects (Box 8) even at low serum lithium levels. The use of slow release forms of lithium carbonate is tolerated by some. Dosing all the lithium at bedtime may help for the side effects to occur when the patient is asleep [96].

Box 8 Side Effects of Lithium and Lithium Toxicity

Neurological
Ataxia, cerebellar dysfunction
Slurred speech
Tremors
Delirium, dementia, memory problems
Parkinsonism
Peripheral neuropathy
Coma
Others
Gastrointestinal symptoms
Polyuria

Information source: Kennedy [97]

Based on published guidelines and the STED-BD report, antiepileptics are preferable

as mood stabilisers for acute treatment and prevention of recurrences in late-life mania and bipolar disorder depression [97]. The anticonvulsant divalproex is considered first choice for treatment and prevention of mania even though infrequent hepatic toxicity is a risk. A therapeutic level is available [97]. Carbamazepine and valproic acid are equally effective as lithium and better tolerated in the elderly. Patients with structural central nervous system disease and mania may respond better to valproate or carbamazepine [98]. Lamotrigine and gabapentin are two other anticonvulsants that have been reported to be effective in the treatment of bipolar disorder.

ii. Antipsychotics: The preferred antipsychotics can be risperidone, quetiapine and olanzapine and in some cases aripiprazole [99]. The prevalence of tardive dyskinesia increases with age. Elderly patients are sensitive to anticholinergic and orthostatic hypotension with low potency antipsychotics as well as the EPS of high potency of neuroleptics [96]. The primary advantage of the atypical antipsychotics (risperidone, clozapine and olanzapine) is a marked reduction or elimination of EPS and the potential for tardive dyskinesia [96].

iii. Calcium channel blockers: They are equally effective as lithium in the treatment of mania, but the elderly are particularly vulnerable to their side effects.

iv. Electroconvulsive therapy: This may be indicated in the severely disturbed older patient when either agitation or aggression becomes extreme [97].

v. Psychosocial interventions: Psychosocial and medication approaches combine well and should often be used together.

Impact

With the increase in life expectancy, there will be an increase in the number of people with mental disorders. The proportion of world's population over the age of 60 will nearly double from 12% to 22% between 2015 and 2050 [100]. Approximately 15% of adults aged 60 and over suffer from a mental disorder, and 6.6% of a disability is due to neurological and mental disorders [100]. It had been estimated that 20.4% of people aged 60 and older met the criteria for mental disorder which included dementia during the previous 12 months [101]. In the United States mental illness is second only to hypertension in prevalence [102], and consequently major depression is a public health problem in the United States [103].

Depression is the most common disorder in individuals 65 years and older and is a leading cause of disability, and 80% of depressed people are impaired in daily functioning [104]. The effects of depression can be overwhelming in every aspect of the patient's life. The physical effects of depression involve the brain, heart and other parts of the body [105]. Major depressive disorder has been shown to predict coronary artery disease, stroke, heart attacks and certain types of cancer [106]. According to the World Health Organization, it will be the second highest rate of disability following cardiac disease by the year 2020 [107]. Depression impacts physically, emotionally and socially. Individuals with major depression have negative emotional states – feeling of helplessness, anxiety and impaired emotional well-being. Families of individuals with depression may have a feeling of guilt, fear, frustration and anger due to the fear of stigma and may feel isolated from friends and community and feel financial strain from medical and mental healthcare costs [107]. Depression and some other psychiatric disorders are themselves associated with increases in the risk of suicide [104].

Impact of major depression on the quality of life and ageing experiences in older adults has been reported [108]. It has also been shown that patients with chronic medical illnesses and co-morbid affective disorder have decreased quality of life with increased somatic symptoms, problems adhering to self-care, increased medical costs and increased rates of mortality [109]. In individuals with chronic illness, untreated depression impairs adherence to treatment [110]. In persons with chronic medical illnesses the lifetime prevalence of affective, anxiety and substance abuse are more prevalent [109]. Depression has a negative impact on co-morbidities such as

diabetes, arthritis and angina [110] and has a close association with stroke [111]. Individuals with major depression have negative emotional states – feeling of helplessness, hopelessness, anxiety and impaired emotional well-being [112].

Major depression can result in enormous economic burden and is an important cause of disability in patients, families and society [113, 114]. Patients with depression and anxiety often suffer from physical symptoms such as headaches, dizziness, nausea, trembling, poor sleep and fatigue and psychological symptoms which include emotional distress, lack of concentration and lack of motivation [115]. They often detach themselves from family and social life, and too many of them commit suicide [116, 117].

Multiple Choice Questions

1. The following medical therapies in depression in the elderly are true, except:
   A. The tricyclics are generally not recommended in the elderly.
   B. SSRI is the first choice in the treatment of depression in older patients.
   C. When tricyclics are initiated, nortriptyline should be used.
   D. If there is a partial response after 4–6 weeks, switch to another drug is recommended.
2. The following in the treatment of depression in the elderly are true, except:
   A. A 'washout period' is not usually required with antidepressants when switching from one to another.
   B. The efficacy of SSRI, MAO inhibitors and tricyclic antidepressants has been shown to be similar.
   C. Venlafaxine, mianserin, nefazodone and tricyclics have blood pressure effects and may be additional risk factor for falls.
   D. For major depression a 6–12 months course is advisable.
3. In the pathophysiology of depression the following are true, except:
   A. The pathophysiology of depression for several years was based on the increase in synaptic connections of serotonin, dopamine and noradrenaline.
   B. The 'late-onset' primary depressive disorder is closely linked to clinical and neuroimagimg evidence of cerebrovascular disease.
   C. Lately there is considerable move to embody structural brain changes – frontal, subcortical and medial temporal.
   D. Major depression is said to be significantly more frequent with right anterior lesions frontal or basal ganglia.
4. The following clinical characteristics of depression are true, except:
   A. Behavioural changes may indicate underlying depressive disorder.
   B. There is a close similarity between depressive pseudodementia and true dementia.
   C. Depression is not accompanied by cognitive symptoms.
   D. Apathy is a common depression.
5. The following are true regarding depression in older adults, except:
   A. Electroconvulsive therapy (ECT) is less often used in older adults than in their younger counterparts.
   B. Older adults with impaired executive function respond poorly to treatment .
   C. Depression in the presence of dementia should not be a contraindication to treatment.
   D. Elderly patients with depression show a wide range of clinical presentation.
6. The following are true of late-onset depression, except:
   A. It is associated with cognitive impairment.
   B. It is pronounced cardiovascular pathology.
   C. It is not associated with vascular dementia.
   D. It is associated with increased hippocampal volume.
7. Which of the following is suggestive of pseudodementia?
   A. Long history of cognitive deficits.
   B. Focal neurological signs.
   C. 'Don't know' answers.
   D. Word finding difficulties are common.

8. The following are true in the treatment of depression, except:
   A. Severe psychotic depression needs referral for ECT.
   B. Antidepressants are the first-line treatment for mild depression.
   C. For major depression a 6–12 months course is advisable.
   D. A 'washout' period is usually required with antidepressants when switching from one to another.
9. The following are true in the treatment of depression, except:
   A. SSRIs are not the preferred first-line antidepressants for the elderly.
   B. If there has been two or more episodes within 5 years, a maintenance treatment up to 3–5 years is necessary.
   C. If there is poor tolerability, switching between drug class is a good option.
   D. At least 6–9 months of treatment is needed for a single episode of depression after remission.
10. In the management of mania the following are true, except:
   A. Careful assessment for an underlying cause is important in mania in old age.
   B. Late-onset bipolar disorder is possible but not the most likely diagnosis in older adults.
   C. Hypomania has the same yardstick as mania but of longer duration and impairs function significantly.
   D. Manic symptoms cover a spectrum of severity from a cyclothymic to severe delusional mania.
11. The following are true with medications used in mania, except:
   A. The primary advantage of atypical antipsychotics is the marked reduction or elimination of extrapyramidal symptoms.
   B. Antiepileptics are preferable to mood stabilisers for acute treatment and prevention of late-life mania.
   C. The elderly have difficulty in tolerating lithium because of the neurological side effects.
   D. ECT is not initiated in severely disturbed older patients when agitation and aggression become extreme.

MCQ Answers

1 = D; 2 = A; 3 = D; 4 = C; 5 = A; 6 = C; 7 = C; 8 = B; 9 = A; 10 = C; 11 = D

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Anxiety and Anxiety Disorders in Later Life

73

Contents

Abstract

Late-life anxiety disorders have been underestimated for several reasons, for example, older persons tend to emphasise their physical complaints and less likely to report psychiatric symptoms. Panic attacks that begin in late life necessitate a search for a depressive disorder, physical illness or drugs that contribute to their presence. Of the anxiety disorders, phobia and general anxiety disorder (GAD) are the two most common in older people. This review summarises the main group of anxiety disorders and their management.

Keywords

Late-life anxiety disorders · Phobia · General anxiety disorder · Obsessive-compulsive disorder · Post-traumatic stress disorder

Introduction

Anxiety disorders are common in later life and are as common as in the young. In about half of the patients, the anxiety disorder comes for the first time in late life and, in the other half, is a persistence of what started in early life. Late-life anxiety disorders have been underestimated for several reasons; for example, older persons tend to emphasise their physical complaints and less likely to report psychiatric symptoms. Panic attacks that begin in late life necessitate a search for a depressive disorder, physical illness or drugs that contribute to their presence [1]. Generalised anxiety disorder (GAD), phobias, panic disorder and obsessive-compulsive disorder (OCD) are the most common late-life anxiety problems seen by the primary-care physician [2]. Of the anxiety disorders, phobia and GAD are the two

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_74

most common in older people [3]. while panic and OCDs are less common [4]. The categories of anxiety disorders in DSM-5 are (1) anxiety disorders, (2) obsessive-compulsive disorders and (3) trauma- and stressor-related disorders.

Clinical Presentations

Generalised Anxiety Disorder (GAD)

GAD is characterised by pervasive and excessive worry regarding a number of events or activities for a period of at least 6 months in duration [5]. The person is unable to control the worry, and it is accompanied by multiple associated somatic symptoms [6]. Most elderly patients with GAD would have had it for many years [4].

Panic Disorder

A panic attack is characterised by a discrete period of fear or discomfort that is unpredictable and not caused in response to the attention of others. Its phenomenology is similar in all respects to that described in the young. Factors that contribute to the onset include stress, medical illness and CNS diseases [7]. Panic attacks are sudden, unpredictable and last minutes to hours. There is no precipitating event. According to DSM-IV [6] dizziness and unsteadiness are among the 13 cardinal symptoms of panic attacks [8]. The panic patients adapt by avoidance of situations and places in which they believe attacks will most likely occur [9]. This maladaptive behaviour finally leads to agoraphobia [10] which is fear in being in places where escape or help would be difficult in the event of a panic attack. In agoraphobia the individual tends to avoid public places such as shopping centres or closed places as in a plane. In the milder form, this may result in self-imposed restriction of certain activities that are associated with anticipation and fear of disability [9]. It is uncommon for panic disorder and OCD to start for the first time in old age [11] (Box 1).

Box 1 Symptoms in Panic Disorder

Palpitations, increased heart rate, sweating
Shortness of breath
Sensation of choking or smothering
Nausea or abdominal distension
Chest pain or discomfort
Dizziness or lightheadedness or faintness
Tingling sensations or numbness
Derealisation (feeling of unreality), Depersonalisation (being detached from oneself), hot and cold flushes
Fear of losing control
Fear of dying

Obsessive-Compulsive Disorder (OCD)

OCD is another anxiety disorder characterised by recurrent obsessions or compulsions sufficient to cause distress and interferes with the individual's routine. It is less common in the elderly, but the annual incidence rises in older women [4]. Obsessions, persistent thoughts, impulses and images which the individual perceives as senseless and inappropriate are recurrent [12]. Compulsions are repetitive behaviours and accompany an obsession and are rituals performed to neutralise or decrease the anxiety-dreaded event. There are many symptoms of the disorder which include checking, washing of hands, cleaning, avoiding, hoarding and being meticulous, among others. Persons with OCD can exhibit a number of these symptoms. The clinical symptoms of OCD are often mixed with other anxiety disorders [13].

Post-traumatic Stress Disorder (PTSD)

PTSD is characterised by symptoms that develop in the aftermath of a distressing or traumatic event that is outside the normal range of human experience. In the elderly, PTSD almost entirely focuses on survivors of earlier-life trauma, such as the Holocaust or combats [14] or after natural disasters. It usually occurs in childhood or young adulthood

and may continue into late life. Physical violence, domestic violence, assault, rape, natural disasters and war experiences are some of the incidents that cause PTSD [15]. The severity in PSTD may be influenced by whether the person is exposed to the trauma once or several times. Symptoms include intrusive symptoms such as nightmares and flashbacks, arousal symptoms such as startling easily and outbursts of anger and avoidance symptoms such as avoiding places among others [15].

Phobias

Phobias are common among the elderly and may present for the first time in old age [4]. Phobias are characterised as excessive or irrational fear of particular situations, places or objects causing the individual to avoid the provoking stimulus. There are an infinite number of phobias. The individual recognises that fear is out of proportion to the danger yet, he/she may go to extraordinary lengths to avoid the stimulus. A common distressing condition is social phobia, which is characterised by persistent anxiety in social situations. Sufferers of social phobia most commonly avoid public speaking and dining in crowded restaurants and often have a fear of losing control of bladder and bowel and are tongue-tied. Phobic elderly patients often feel shame, isolation and excessive dependence on caregivers [14]. High degree of comorbidity with psychiatric disorders including mood and anxiety disorders and substance abuse are associated with social phobia [16]. In the elderly, these phobias prevent them from seeking help; because of this, the person is often mistaken as uncooperative.

Somatisation disorders are now classified separately from anxiety disorders, and some of these may overlap with GAD and may be diagnostically difficult to distinguish [17]. Hyperventilation is a common behavioural disturbance associated with anxiety disorder in particular with panic attacks [18]. Hyperventilation can be either the initial trigger of a panic attack or alternatively a behavioural response to a fearful situation [19].

Diagnosis

Recognising an anxiety disorder in older persons poses several challenges. Separating a medical condition from physical symptoms of an anxiety disorder is complicated in the elderly. GAD and panic disorder usually present with multiple somatic symptoms. Patients with these disorders complain of diverse multisystem symptoms and such physical symptoms as dizziness. GAD can be distinguished from panic disorder if the person has frequent panic attacks and agoraphobic symptoms. Many patients with GAD may occasionally have panic or anxiety attack, and these patients should be considered as GAD [17]. The DSM-IV [84] requires four or more of the following symptoms reaching a peak within 10–15 min to diagnose panic disorder. The distinction between GAD, OCD and PSTD is not difficult by definition [17]. The cardinal symptoms of GAD may overlap with social phobia particularly if the social phobia is more general [17].

Diagnosing anxiety in a person with dementia can be difficult for agitation, impaired memory or fears in a demented person can be misinterpreted as anxiety. There is a high incidence of depression with anxiety. Depression and anxiety go together in the elderly. About 85% of patients with depression have significant anxiety and 90% with anxiety disorder have depression [20].

Treatment

Anxiety disorders respond well to treatment. The specific treatment will depend on the type of anxiety disorder and its severity. The different treatments are listed in Box 2. In cognitive-behavioural therapy (CBT), the irrational beliefs and negative thinking patterns that are inciting the anxiety are identified and challenged. CBT comprises anxiety management, cognitive restructuring and behavioural strategies [21]. With exposure therapy the patient confronts his or her fears in a safe and controlled environment, and through repeated exposures, they gain control of the situation. Complementary treatment includes exercise, relaxation techniques and hypnosis. Pharmacological agents used are

anxiolytics, buspirone, antidepressants and beta-blockers. Pharmacotherapy and cognitive-behavioural therapy are the most effective forms of treatment. Physicians should consider non-pharmacological interventions first because of the hazardous side-effects of many antianxiety agents [14]. For anxiety disorders like GAD and OCD, medication may be necessary for longer periods, whereas for anxiety disorders such as phobias or social anxiety disorder, medication may be required from time to time.

Box 2 Treatments in Anxiety Disorders
Cognitive-behavioural therapy
Exposure therapy
Psychosocial supports
Pharmacological therapy
Complementary treatment

Generalised anxiety disorder (GAD). Late-onset GAD. The primary pharmacological treatment is antidepressant therapy for late-onset GAD is usually associated with depressive illness. GAD and agoraphobia account for most cases of anxiety in late life. Most elderly with agoraphobia do not give a history of panic attacks; exposure therapy is the preferred treatment for agoraphobia without panic [22]. Short-acting benzodiazepines such as lorazepam, oxazepam and temazepam are drugs of choice [14]. Buspirone may also be used in this condition [14].

Panic disorder. It is difficult to envisage a neurotransmitter system involved in panic disorder. This may be the reason why there is no single effective therapy and there are no pharmacological treatment studies specific to the elderly [14]. A number of drugs have been used such as tricyclics, monoamine oxidase inhibitors (MAOI), selective serotonin receptor antagonists (SSRI) and benzodiazepines used singly or in combination. All appear equally effective [14]. The choice of agent is based on patient tolerance and side effect profile. The cognitive and behaviour therapy either alone or in combination with pharmacotherapy has been found to be effective [23].

Obsessive-compulsive disorder (OCD). Case series studies and case reports have indicated that OCD and panic disorder in the elderly can benefit from pharmacological and cognitive-behaviour treatment, but the extent of the response is not known [11]. In the elderly patient, these conditions may be responsive to SSRI and require dose adjustment and monitoring [14].

Post-traumatic stress disorder (PTSD). Tricyclics and MAOI antidepressants have been found to be useful in diminishing nightmares and intrusive thoughts, and fluoxetine has been effective for avoidant symptoms [24]. Propranolol, valproate and carbamazepine are other potentially useful drugs [14, 25].

Phobias. Cognitive-behavioural therapy is recommended as treatment for phobias [16] in combination with benzodiazepines for special phobias.

Impact

Anxiety disorders cost the United States more than $42 billion a year, about one-third of the total health bill [26]. All anxiety disorders markedly reduce quality of life and cause problems in significant relationships [27], social activities and daily functioning. Living with a person with anxiety can be demanding, causing considerable strain on spouse, family and social relationships [28] (Box 3).

Box 3 Key Points: Late-Life Anxiety Disorders
Generalised anxiety disorder (GAD), phobias, panic disorder and obsessive-compulsive disorder (OCD) are the most common late-life anxiety problems seen by the primary-care physician [2].

Most elderly patients with GAD would have had it for many years [4].

It is uncommon for panic disorder and OCD to start for the first time in old age [11].

Physical violence, domestic violence, assault, rape, natural disasters and war experiences are some of the incidents that cause PTSD [15].

Phobias are common among the elderly and may present for the first time in old age [4].

(*continued*)

Box 3 Key Points: Late-Life Anxiety Disorders (continued)

Physicians should consider non-pharmacological interventions first because of the hazardous side-effects of many anti-anxiety agents [14].

Multiple Choice Questions

1. The following are true of anxiety and anxiety disorders, except:
   A. In about half the patients, the anxiety disorder comes for the first time in late life.
   B. Of the anxiety disorders, phobia and GAD are the two least common in older people.
   C. OCD is less common in the elderly, but the annual incidence rises in older women.
   D. Most elderly patients with GAD would have had it for many years.

MCQ Answers

1 = B

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Late-Life Psychosis

74

Contents

Abstract

The more notable ones are delusional disorder, schizophrenia and psychosis in patients with dementia or depression. This article will focus on delusional disorder and late-onset schizophrenia. Paranoid states and schizophrenia could occur for the first time in late life, and the two conditions have been combined as late-onset schizophrenia and paranoid states.

Keywords

Delusional disorder · Late-onset schizophrenia · Paranoid states · Psychosis

Introduction

In the elderly, psychosis can present in several ways [1]. These may include delirium, affective illness, dementia, schizophrenia, other psychotic disorders, substance abuse [2], delusional disorder [1] and specific brain disorders, for example, tumour [3]. The more notable ones are delusional disorder, schizophrenia and psychosis in patients with dementia or depression [1]. This article will focus on delusional disorder and late-onset schizophrenia.

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_76

Late-Life Delusional (Paranoid) Disorders

Delusional disorders previously called paranoid disorders are characterized by the presence of false beliefs or delusions which are held despite rational grounds to the contrary. Paranoid ideation was found in 6.3% of a sample of 1,420 elderly people [4]. Prevalence rates among older adults without cognitive impairment were found to be as high as 14.1% for suspiciousness, 6.9% for paranoid ideation and 5.5% for delusions [5]. About 34.6% fulfilled the criteria for paranoid disorder in patients with dementia of moderate severity [6]. In one study, only 1/10 of the older Whites expressed paranoid ideation or psychotic symptoms compared to 1/4 of the older blacks [7]. The prevalence of paranoid personality disorder is 0.5–2% in the general population and 2–10% in psychiatric outpatients [8]. In another study, the prevalence was around 1.3% in the community [9] rising to 10% in psychiatric out patients [10].

Paranoid symptoms may be a manifestation of medical, neurological, psychiatric or medication-induced illness [11] and may surface as a primary symptom in many psychiatric and physical disorders or secondary to other disorders that occur in the elderly. The paranoid symptoms that may be secondary occur in disorders such as organic brain syndrome – dementia, delirium, mood disorders or cerebrovascular pathology. The elderly are at greater risk of developing persecutory thoughts because of medical illness, visual and hearing impairments, social isolation and ageing process itself [12].

Overview of Clinical Presentations

i. Paranoid personality disorders

In the community, the prevalence of paranoid personality disorder is about 1.3% [9] increasing to 10% in psychiatric outpatient [10]. Individuals with paranoid personality disorder have extreme suspiciousness of others such that their motives are interpreted as malicious [13] and distrustful. It is more common in the males. It first manifests in childhood and adolescence and characterized by hypersensitivity, poor performance in school, poor peer relationships, eccentricity and bizarre ideas. Those who enter late life with paranoid personality disorder have poor interrelationship because of their suspiciousness and combative nature. Their suspiciousness and paranoia may increase and evolve into a delusional disorder. They become extremely sensitive to any change in situations and react with hostility. As a result, they become prone to violence [14] and antisocial behaviour [15]. Furthermore, social isolation and communication impairments such as impaired hearing result in paranoidal tendencies. Transient psychotic episodes can occur in persons with delusional personality in response to stress.

ii. Delusional (paranoid) syndromes

Delusional syndromes are characterized by persistence of one or more false beliefs. It begins in the mid- or late adult life [16], and the severity of the delusions varies over time. The delusions are non-bizarre in character and involve situations that occur in real life such as being poisoned, or infected, being loved from a distance, or being deceived by a lover or spouse among others. The presence of bizarre delusions rules out the diagnosis. They do not generally behave in an abnormal manner and continue to function normally, occupationally and socially [17]. When dysfunction occurs, it is due to the direct response to the delusions. There are six subtypes according to DSM-V [18], and they are recognized by their specific themes.

Subtypes:

i. Grandiose – have an exaggerated or ostentatious sense of power, knowledge or individuality.
ii. Erotmanic – a belief that someone important is in love with the individual and often resulting in stalking or attempting to contact the person.
iii. Jealousy – believes that the spouse is unfaithful. Delusions concerning infidelity of the spouse (Othello syndrome, delusional jealousy or morbid jealousy) can be one of a

number of manifestations of paranoid psychosis, or it may occur as a monosymptomatic delusional belief [19]. It can occur in organic psychosis, paranoid disorders, alcohol psychosis, schizophrenia and to a lesser extent affective disorder [20]. The occurrence of delusional jealousy in the elderly psychiatric population is 1.4% [21].

iv. Persecutory – someone is planning to harm them or spying on them.
v. Somatic – a belief that he or she have a physical defect or medical problem.
vi. Mixed – having features of more than one subtype.

Other delusional-related disorders:

i. Misidentification

It had been customary to consider misidentification as a delusion [22, 23], and the psychiatric literature abounds with the term 'delusional misidentification syndromes'. Misidentification of self, others, places, time and objects presenting with a variety of symptoms has been identified [24], and misidentification syndromes are defined as (i) Capgras type, i.e. misidentification of people, (ii) 'phantom boarder', false belief of imagining people living in the house, (iii) 'mirror image' misidentifying their own image as someone else and (iv) 'TV sign' misidentifying TV images as real [25]. It occurs in a large number of conditions, medical, psychiatric and neurodegenerative including the dementias. In Alzheimer's disease, the incidence varies from 29% to 34% [25]. Distinctions between the different types of misidentification may be unnecessary in patients with significant cognitive impairment as in dementia of the Alzheimer type [26]. There is a highly significant association between misidentification and accusatory behaviour and a likely relationship to other behaviours such as frustration, hallucinations, aggression and violence [27, 28].

ii. Delusional parasitosis

Delusional parasitosis is a belief that the skin is infested with worms, insects or organisms. It could be produced by a variety of organic processes: toxic, metabolic and structural disorders. Delusional parasitosis may occur as a monosymptomatic delusional belief or by one of a number of manifestations of paranoid psychosis.

Late-Onset Schizophrenia

Paranoid states and schizophrenia could occur for the first time in late life, and the two conditions have been combined as late-onset schizophrenia and paranoid states [29]. A clinical follow-up and genetic study concluded that late paraphrenia should be regarded as the mode of manifestation of schizophrenia [30]. British and American psychiatrists used the term 'late-onset schizophrenia' interchangeably with late paraphrenia or a generic term for both [31]. Late paraphrenia is a British concept that includes all delusional disorders starting after the age of 60 years [31].The current trend to include 'late paraphrenia' into the diagnosis of schizophrenia or delusional disorder has poor empirical and theoretical basis [32]. The term 'late-onset schizophrenia' (LOS) has largely supplanted 'paraphrenia' [33], and LOS is defined as occurring after the age of 45 years [3, 33]. It has been proposed that late-onset schizophrenia is a subtype of schizophrenia [34] and is predominantly a paranoid subtype [3, 35, 36] though others have found it to be no more of the paranoid subtype [34, 37]. The DSM-IV has not included a category as 'late-onset schizophrenia' nor an age criterion for the diagnosis of schizophrenia [34, 38]. A new entity, the 'very late-onset schizophrenia-like psychosis'(VLSOP) replaced 'late paraphrenia' and grouped schizophrenia, delusional disorder and paranoid psychoses with age of onset after 60 years [39].

Notable clinical features of late-onset schizophrenia include persecutory delusions and auditory hallucinations [3]. Although both EOS and LOS are similar in respect to fundamental clinical features, there are several distinctive characteristics with LOS [34]. Similarities and differences between late-onset schizophrenia and early-onset schizophrenia are shown in Table 1.

Treatment

Multiple double-blind trials have shown that risperidone and olanzapine are of benefit in treatment of older adults with psychotic symptoms [42, 43] (Table 2).

Table 1 Similarities and differences between late-onset and early-onset schizophrenia

	LOS	EOS
Age of onset	>45 years	<45 years
Male/female	1:2–10	1.4:1
Family history	10–15%	10–15%
Childhood maladjustment	Similar	Similar
Clinical features		
Positive symptoms	Less severe	Severe
Negative symptoms	Less severe	Severe
Cognitive deficits	Same	Same
Severity	Less severe	Severe
Learning and abstraction impairment	Less severe	Severe
Chronicity of course	Same	Same
Neuroimaging; MRI		
Thalamic volume	Larger	Smaller
Treatment		
Antipsychotic dose requirement	Lower	

Information sources: McClure et al. [3]; Jeste et al. [35, 36];Vahia et al. [37]; Brodaty et al. [40]; Corey-Bloom et al. [41].

Paranoid Symptoms Secondary to Other Disorders

Some types of delusions are manifestations of organic disorders and mood disorders. Delusions occurring in organic disease are of four types: simple persecutory, complex persecutory, grandiose and those associated with special neurological deficits [19].

Dementia: Dementia may progress insidiously, and very often it is the behavioural and psychiatric manifestations that bring the patient to the clinician's notice. Dementia syndrome is commonly associated with behavioural and psychiatric symptoms. Delusions and hallucinations increase with increasing age [44]. Greater severity of dementia has been stressed as a predisposing factor for its development [45]. Some found that it was associated with moderate and severe dementia [46]. Others found no difference across the three levels of dementia severity [47, 48] and no difference in the frequency of delusions and hallucinations in patients with Alzheimer's disease and vascular dementia [49]. In one study, 22% of dementia patients had simple persecutory delusions or delusions of theft or suspiciousness, and 13% had more complex persecutory delusions [50].

Delirium: Delirium is an acute disorder and may be due to a range of conditions including infection, drug intoxication or withdrawal, metabolic abnormalities and cerebral disorders. It is characterized by a reduced level of consciousness, shifting attention, inability to concentrate,

Table 2 Atypical antipsychotics commonly used in the elderly

Medication	Initial dose mg/d	Standard average daily mg	Maximum daily dose mg	Dose frequency	Side effects
Risperidone	1–2	2–6	6–8	qd/bid	Dose-related EPS
Olanzapine	5–10	15–30	40	qd	Sedation, weight gain
Quetiapine	25–30	300–600	800–1,000	bid/tid	Sedation
Clozapine	25–50	50	300–600	qd/bid	Sedation
					Agranulocytosis[a]
Ziprasidone	40–80	80–160	160	bid	QTc prolonged action

[a]Mandatory monitoring weekly of WBC for 6 months thereafter biweekly

memory impairment, incoherent speech, delusions and visual hallucinations.

Cerebral pathology: Patients with psychotic symptoms in old age demonstrate neurological soft signs indicating brain disease which is a critical factor in its causation [51]. Neuroimaging and neuropsychological studies suggest the existence of an organic substrate in most cases of late paraphrenia and only minor abnormalities in late-onset schizophrenia [31]. Late-life psychosis is often associated with cerebrovascular disorders and cerebral atrophy [52] (Table 3).

Treatment

There should be a close working relationship between geriatrician and primary care physician and a trusting and supportive relationship between patient and primary care physician. The primary care physician should establish a relationship with key members in patient's environment, the most important being family.

Cognitive behavioural therapy can be used to treat delusions and paranoia [57] as it helps to reduce sensitivity to criticisms, restructuring beliefs with the goal of targeting delusional thoughts. Often these patients with paranoidal symptoms exhibit hostility and pharmacological therapy have proven effective. Elderly patients are particularly sensitive to anticholinergic and orthostatic hypotension associated with low-potency antipsychotics and extrapyramidal symptoms (EPS) of high-potency neuroleptics. The atypical antipsychotics are useful for they have the advantage of reducing or eliminating EPS and the potential for tardive dyskinesia. The prevalence of tardive dyskinesia increases with age and bipolar elderly patients have a high rate of tardive dyskinesia [58].

Impact

The more notable psychosis of late onset is delusional disorder, schizophrenia and psychosis in patients with dementia or depression. The psychotic disorders comprise about one-third of severe mental disorders [59]. Poor physical health outcomes and comorbidities are relatively common in people with psychotic illness [60]. Psychosis in late life can impose enormous costs to the affected individuals, their caregivers and society [61] (Box 1).

Table 3 Clinical and pathological correlates in secondary paranoidal disorders

Age years	Sex	Presenting symptoms	CT Scan findings	Diagnosis
82	F	Visual, auditory, hallucinations, paranoid delusions	Multiple lacunar infarcts	late paraphrenia
93	M	Persecutory and fantastic delusions	Right basal ganglia infarct	Paranoid delusional
				Disorder
93	M	Marital infidelity	Left pontine infarct	Morbid jealousy
88	F	Delusional belief persecutory in nature	Small infarcts and white matter disease	Paranoid delusional disorder
77	M	Persecutory delusions	Enlargement of ventricles	Normal pressure hydrocephalus
		Paranoid ideas about family members		
78	M	Paranoid ideation	Enlargement of ventricles	Normal pressure
		Spouse after his money		
88	F	Trying to poison her	White matter changes	Binswanger's disease
		Religious overtones	Focal densities	
		Church against her		
69	F	Crawling feeling under skin	Temporo-occipital infarction	Delusional parasitosis
65	F	'Infested with tiny bugs'	Temporo-occipital infraction	Delusional parasitosis

Information sources: Nagaratnam, Nagaratnam [50], Nagaratnam and Pathma-Nathan [53]; Nagaratnam et al. [54, 55]; Nagaratnam and O'Neill [56]

Box 1 Key Points. Late-Onset Psychosis

These may include delirium, affective illness, dementia, schizophrenia, other psychotic disorders, substance abuse [2], delusional disorder [1] and specific brain disorders, for example, tumour [3].

Paranoid symptoms may be a manifestation of medical, neurological, psychiatric or medication-induced illness [11] and may surface as a primary symptom in many psychiatric and physical disorders or secondary to other disorders that occur in the elderly.

Individuals with paranoid personality disorder have extreme suspiciousness of others such that their motives are interpreted as malicious [13] and are distrustful.

Delusional syndromes are characterized by persistence of one or more false beliefs. It begins in the mid-or late adult life [16].

Paranoid states and schizophrenia could occur for the first time in late life, and the two conditions have been combined as late-onset schizophrenia and paranoid states [29].

A new entity, the 'very late-onset schizophrenia-like psychosis'(VLSOP) replaced 'late paraphrenia' and grouped schizophrenia, delusional disorder and paranoid psychoses with age of onset after 60 years [39].

Multiple double-blind trials have shown that risperidone and olanzapine are of benefit in treatment of older adults with psychotic symptoms [42, 43].

Multiple Choice Questions

1. The following are true in relation to late-life psychosis, EXCEPT:
   A. Paranoid symptoms may be a manifestation of medical, neurological, psychiatric or medication-induced illness.
   B. Delusional syndromes are characterized by persistence of one or more false beliefs.
   C. Paranoid states and schizophrenia do not occur for the first time in late life.
   D. Patients with psychotic symptoms in old age demonstrate neurological soft signs indicating brain disease.

MCQ Answers

1 = C

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Suicide in the Elderly

75

Contents

Abstract

Depression is a significant risk factor for suicide in late life and represents 85% of older adults dying by suicide. There is a strong association between physical illness and suicide among the elderly. Cancer, prostate disorder, chronic pulmonary disease, and psychiatric illness appear to be associated with suicide in the elderly. Older men have a significantly higher rate than women for committing suicide. The male suicide rate increases with age peaking in the late 1940s and then falling in the 1980s. The review provides an overview of the prevalence of suicide in the elderly followed by assessment of suicide risk and prevention.

Keywords

Suicide in late life · Male suicide rate · Assessment of suicide risk · Suicidal intent

Introduction

Depression is a significant risk factor for suicide in late life and represents 85% of older adults dying by suicide [1]. Depression increases the risk of mortality among subjects about 1.5–2.0 times as compared with those without depression [2, 3]. It has been reported that baby boomers have three to four times the rate of emotional disorders (depression, suicide, anxiety, alcohol-drug abuse) than are found in today's elderly population [4].

There is a strong association between physical illness and suicide among the elderly [5, 6]. The prevalence varies widely from 34% to 94% [7], and a report noted serious physical illness in 56% of those who committed suicide compared to 16% in the control group [8]. Cancer, prostate disorder, chronic pulmonary disease, and psychiatric illness appear to be associated with suicide in the elderly [9].

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_75

Suicidal intent is a good predictor of subsequent completed suicide [10]. Those who scored highly for suicidal intent were found to be at higher risk of complete suicide within a year of attempt [11]. There is higher level of intent and more planning in suicidal deaths of older adults compared to their younger counterparts [12]. Suicide rates among the elderly Whites increase with age and are significantly higher than among elderly Black [13]. Older men have a significantly higher rate than women for committing suicide. The male suicide rate increases with age peaking in the late 1940s and then falling in the 1980s [14].

Assessment of Suicidal Risk and Management After Suicidal Attempt

There are a number of scales available for predicting suicidal risk. Beck's Suicidal Intention Scale [15] and the Pierce Suicide Intent Scale are most widely used scales. There are about 15 items looking at the patient's thoughts and emotions at the time of suicidal attempt and circumstances around the attempt [16]. Assessment and management of suicidal ideation and behavior is of particular relevance to the primary care physician, for many patients visit the physician shortly before committing suicide [17].

Assessment after suicide attempt requires an understanding of the demographic variables. A thorough history should include psychiatric illness; substance abuse including prescription and over-the-counter drugs; history of medical illnesses; past history of suicidal attempts; personal history of stressful life events, financial, and social resources; a family history of psychiatric illness and suicides; and evaluation of physical and mental status with emphasis on mood and affect. The PATHOS score may be used to identify high-risk patients after an overdose [18].

Individuals who have attempted suicide are at increased risk of dying by suicide later, and 20% of them who attempted suicide will be trying again in the future [19]. An assessment of the risk of suicide requires accurate knowledge of suicide ideation, suicide plans, suicide intent, methods, previous suicidal attempts [20], and barriers to committing suicide. Substantiation of suicidal intent in an individual who has made a suicidal attempt constitutes the seriousness of the act. Protective factors (Box 1) heighten resilience and may offset risk factors. They include no plan, intent, or access to means, good social support, close family relationship, strong religious and cultural factors, and ongoing medical and mental care relationship [21]. If the individual expresses suicidal ideation and has a suicide plan, attempt involved high lethality and access to lethal means, and poor or no social support, he or she should be hospitalized [22]. An intoxicated patient should not be discharged [23]. If the individual has no access to lethal means and has good social support, he or she should be evaluated for psychiatric disorders or stressors and treated accordingly. If there is no response, a second opinion should be obtained [23].

Box 1 Protective Factors for Suicide

Effective clinical care for mental, physical and substance abuse disorders

Easy access to a variety of clinical interventions and support for help seeking

Restricted access to highly lethal means of suicide

Strong family and community support

Support through ongoing medical, mental health care relationships

Skills in problem solving, conflict resolution and nonviolent handling of disputes

Cultural and religious beliefs that discourage suicide and support self preservation

Information sources: SPRC [21]; US Public Health Services [25]

Strategies for Suicide Prevention in the Elderly

Prompt assessment and appropriate psychosocial intervention can save the life of an older person. Both in the primary and secondary care settings,

early recognition and treatment of mental illness especially depression can prevent suicide [24]. Other strategies include the development of community-based outreach services and public health measures to reduce the availability of lethal methods [24].

Impact

Suicide rates increase progressively with age. The highest suicide rates occur among persons aged 65 years and older and are about 50% higher than in young people. There is a strong association between physical illness and suicide among the elderly [6, 7]. A recent study has shown a close relationship between low self-esteem and suicidal tendencies. Low esteem is closely related to depression, feeling of hopelessness, and suicidal ideation [26] (Box 2).

Box 2 Key Points. Suicide in the Elderly

Suicide can be defined as an act of deliberately or intentionally causing one's own death

Depression is a significant risk factor for suicide in late life and represent 85% of older adults dying by suicide [1].

The male suicide rate increases with age peaking in late 1940s and then falling in the 1980s [14].

Individuals who have attempted suicide are at increased risk of dying by suicide later and 20% of them who attempted suicide will be trying again in the future [19].

There is a strong association between physical illness and suicide among the elderly [5, 6].

There is higher level of intent and more planning in suicidal deaths of older adults compared to their younger counterparts [12].

The PATHOS score may be used to identify high risk patients after an overdose [18].

An intoxicated patient should not be discharged [23].

If the individual has no access to lethal means, has good social support he or she should be evaluated for psychiatric disorders or stressors and treated accordingly.

If there is no response a second opinion should be obtained [23]

Multiple Choice Questions

1. The following are true of suicide in the elderly EXCEPT:
   A. The suicide risk decreases progressively with age.
   B. Suicide attempts in the elderly are more lethal than in the young.
   C. Widowers are significantly more at risk than elderly widows.
   D. Suicide is generally associated with major depression especially in elderly males.
2. The following are true of suicidal behavior EXCEPT:
   A. Suicide intent is a good predictor of subsequent completed suicide.
   B. Individuals who have attempted suicide are at increased risk of dying by suicide later.
   C. Eighty percent of those who attempted suicide will try again in the future.
   D. Protective factors may offset suicide risk factors.
3. The following are true with suicidal behavior in the older adult EXCEPT:
   A. Among the older patients, suicidal behavior is more likely to be fatal.
   B. Older patients are more likely to visit their doctor shortly before death.
   C. Abuse of alcohol increases the risk of suicide in older patients.
   D. Lower levels of intent and planning in suicidal deaths in older patients compared to younger patients.
4. What percentage of the elderly contact their family physician in a month before completed suicide?
   A. 70%
   B. 50%
   C. 35%
   D. 5%

5. The following are true of suicide in the elderly, EXCEPT:
   A. Eighty percent of the older people who committed suicide suffered from depression.
   B. The females are 4 times more likely to commit suicide than males.
   C. Fifty percent of the older people contact their doctor in the month before completed suicide.
   D. Living alone, bereavement, and recently separated from partner are high-risk factors for suicide in the elderly.

MCQ Answers

1 = A; 2 = C; 3 = D; 4 = B; 5 = B

Short Answer Questions

1. List four risk factors for suicide in the elderly.

SAQ Answers

1. Is higher in men more than in women.
2. Living alone is an important contributing factor.
3. Major depression and other mood disorders are common risk factors.
4. Bereavement especially in men is considered a risk.
5. Substance abuse accounts for as many suicide deaths as for the younger age group.

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Substance Abuse in the Elderly

76

Contents

Abstract

There are two different groups in terms of age of onset of alcohol drinking among the older drinkers. The 'early-onset' alcoholics begin drinking in their early twenties. The 'late onset' tend to be highly educated, and stressful life event frequently precipitates or exacerbates their drinking. Women are more prone to late-onset alcoholism than men.

Keywords

'Late-onset' alcoholics · 'Early-onset' alcoholics · Chronic alcoholism · Prescription and over-the-counter drugs · Baby boomers

Introduction

There are two different groups in terms of age of onset of alcohol drinking among the older drinkers. The 'early-onset' alcoholics begin drinking in their early twenties. They are seen with the common stereotype of chronic alcoholism and struggle with multiple medical, psychological and social problems, and often there is a family history of alcoholism. They impair their health and personal relationships severely and do not reach old age for obvious reasons and suffer from psychiatric illness, cirrhosis and organic brain syndrome [1, 2]. The 'late onset' tend to be highly educated, and stressful life event frequently precipitates or exacerbates their

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_72

drinking [1]. They drank rarely but increased their drinking either due to changes brought about by the ageing process or encountered problems they no longer can handle such as major physical or lifestyle changes and often triggered by health problems, death of spouse, financial worries or sleeplessness and increase the amount of alcohol they consumed in earlier life. They are more receptive to treatment and more likely to recover spontaneously from alcoholism [1]. Older men are more likely to be married, divorced or separated, and older women had a higher rate of widowhood [3]. Elderly persons with higher incomes consumed more alcohol than those with lower incomes [4], and several studies have shown that the quantity and frequency of alcoholic consumption were higher in elderly men than in elderly women [5] compared to alcoholics with late onset and with early onset and found the former had lower actual alcohol consumption and fewer previous detoxifications and a higher rate of abstinence in a 12-month follow-up. Women are more prone to late-onset alcoholism than men and develop alcohol-related health problems more sooner and had problematic use of prescribed psychoactive drugs than alcohol [3].

Alcohol Withdrawal Syndromes

The reduction or cessation of alcohol results in symptoms and signs of alcohol withdrawal. Alcohol withdrawal manifests as nausea, vomiting, diarrhoea, sweating, tremors or tremulousness, tachycardia, elevated blood pressure, anxiety, agitation, sleeplessness, visual, tactile or auditory hallucinations and seizures [6] (see Box 1).These symptoms occur 6–24 h after the last drink [7], and it is crucial to recognize these as alcohol withdrawal so that early and appropriate treatment may be instituted. About 5–10% of the alcoholics develop delirium [7] during withdrawal, and it occurs usually 48–72 h after cessation of alcohol and is characterized by increasing confusion, clouding of consciousness, hyperactivity and increased pulse rate and temperature. A persistent resting coarse tremor of the hand develops sometimes involving the trunk and head. Older patients have an increased risk of developing delirium and have prolonged stay in hospital, higher risk of institutionalization and higher mortality. Seizures may complicate alcohol withdrawal [8]. Delirium should tend to resolve within 12–24 h, but if there is no substantial improvement, an alternate diagnosis must be thought of.

Box 1 Symptoms and Signs in Withdrawal Syndrome

Anxiety, agitation
- Tremors, tremulousness
- Sweating
- Tachycardia, palpitations
- Poor sleep
- Elevated blood pressure
- Visual/tactile/auditory hallucinations

Treatment of Withdrawal Syndrome and Delirium Tremens

Initially a medical evaluation is necessary to exclude or detect intercurrent illness that may complicate withdrawal. For simple alcohol withdrawal, benzodiazepines are the mainstay of drug treatment. The choice of the benzodiazepines will depend on the age of the patient and the presence or absence of liver disease. Some experts recommend shorter-acting benzodiazepines for the elderly patient for the longer acting can cause excessive sedation and serious side effects [9] but provide less frequent dosing and when the dose is tapered smoother return of serum levels. They can be administered as a fixed schedule or as symptoms occur, the latter regimen requires less medication for detoxification. Concomitantly the patient should receive vitamin supplements especially thiamine, together with correction of electrolytes, maintenance of nutrition and fluid balance and general supportive care.

Long-Term Treatment

This includes coordinated care with multidisciplinary team members. Various types of psychotherapy have been recommended, but it is

believed group therapy is better than one-on-one therapy. Alcoholics Anonymous approach has proved beneficial for many alcoholics. Disulfiram (Antabuse) is not recommended for use in the elderly because of adverse effects [9, 10].

Complications

Excessive alcohol consumption is a major cause of physical ill-health as well as social and emotional problems. The National Health and Medical Research Council (NHMRC) [11] recommends that men consume less than four standard drinks (40 g alcohol) per day and women less than two standard drinks (20 g alcohol) per day. In the elderly the use and abuse of alcohol often results in cirrhosis and other liver diseases, malnutrition, falls and fractures, dementia, delirium, anaemia, cardiomyopathy and poor compliance with medications. Alcohol is toxic to almost every organ system.

Box 2 Neurological Complications of Chronic Alcohol Toxicity

Wernicke's encephalopathy
- Korsakoff's psychosis
- Sensorimotor peripheral neuropathy
- Myopathy
- Cerebellar degeneration
- Demyelinating disorders
- Optic neuropathy
- Marchiafava–Bignami

Neurological complications of chronic alcohol toxicity are listed in Box 2. Wernicke's syndrome is associated with long-term use of alcohol. It is due to thiamine deficiency and alcohol is the most common cause. The term Wernicke's syndrome is used to describe the clinical triad of confusion, ataxia and ophthalmoplegia. It may resemble the manifestations of acute alcoholic intoxication but in the case of Wernicke's the symptoms persist after intoxication wears off.

Korsakoff's syndrome is characterized by persistent learning and memory deficits and sometimes confabulation [12]. The memory deficits are for current and recent events more than for remote which the patient tries to compensate by confabulation [12]. It often follows Wernicke's encephalopathy. It is an alcohol-induced persistent amnestic disorder, and about 80% of the patients with chronic Korsakoff's never recover fully.

Cerebellar degeneration can occur with Wernicke's or by itself. It is characterized by truncal ataxia. Alcohol-related myopathy can be acute or chronic. The latter presents with proximal muscle weakness. Marchiafava–Bignami is a demyelinating disease involving the corpus callosum and extending to involve the centrum ovale bilaterally. The patient becomes agitated and confused, and the disease may progress to dementia, paralysis, frontal release, coma and death.

Problem of Detection and Identification

The common definition of alcohol abuse and dependence may not apply as readily in older persons who have retired and have few social contacts [13]. Current diagnostic criteria for alcohol use disorders may not be appropriate for elderly people, and alcohol misuse is not recognized by healthcare professionals because of their inadequate training and negative perspective [14]. There is a wider fluctuation of symptoms over time in the elderly alcoholics causing difficulty in clinical recognition of substance abuse, and furthermore this is compounded by a greater level of co-morbidity and medical, psychiatric and social dysfunction [15]. More often the elderly present with health-related problems rather than behavioural. Depression, anxiety, confusion or forgetfulness, frequent falls and urinary incontinence are some of the signals that may be ignored.

There are several screening instruments that can be used by family physicians to identify patients who have problems related to alcohol. However they may not be appropriate for the elderly. The geriatric version of the Michigan Alcoholism Screening Test (MAST- G) [16] has high specificity and sensitivity with older people in a wide range of settings including primary care surgeries and nursing homes. It has 10 questions, and scoring

2 or more 'yes' response is indicative of alcohol problem. The revised version is a 22-question self-test. The Alcohol Use Disorders Identification Test was developed by the WHO in 1982 [17] as a simple way to screen and identify people at risk of developing alcohol problems [18].

Impact

Alcoholism in the elderly for the most part remains unrecognized; as the baby boomer generation reach ageing levels, the situation could reach a healthcare crisis. Age-related physiological changes increase the susceptibility to deleterious effects of alcohol and other illicit substances [19]. An estimated 10% of all cases treated by geriatric mental health facilities are alcohol and substance abuse and together with mental health problems are concurrent and interactive. Substance abuse in the elderly is most often associated with alcohol misuse and abuse, prescription and over-the-counter drugs. They are seen with the common stereotype of chronic alcoholism and struggle with multiple medical, psychological and social problems. In the elderly alcoholism causes and complicates medical conditions by creating unsafe medication, interactions and increasing the risk of falls, confusion and premature mortality [20]. In the elderly symptoms of alcohol withdrawal are often missed and attributed to a cause other than to alcohol [19]. Because of the use of multiple medications and sensitivity to their effects due to ageing, older adults are particularly at risk of unintentional misuse of medication [20]. In the United States 2.5 million older adults have problems related to alcohol [21]. Alcohol problems are common in depression with worse outcomes with respect to suicide, social functioning and healthcare utilization [22]. One of the social effects of depression is substance use and abuse. The number of older adults requiring treatment for substance abuse is estimated to increase from 1.7 million in 2000 and 2001 to 4.4 million in 2020 [23] (Box 3).

Box 3 Key Points. Substance Abuse in the elderly

The 'late onset' tend to be highly educated, and stressful life events frequently precipitate or exacerbate their drinking [1].

Substance abuse in the elderly includes alcoholism, to a lesser degree illicit substances, prescription medications and over-the-counter medications.

Some experts recommend shorter-acting benzodiazepines for the elderly patient for the longer acting can cause excessive sedation and serious side effects [9] but provide less frequent dosing and when the dose is tapered smoother return of serum levels.

Disulfiram (Antabuse) is not recommended for use in the elderly because of adverse effects [9, 10].

Korsakoff's syndrome is characterized by persistent learning and memory deficits and sometimes confabulation [12].

There is a wider fluctuation of symptoms over time in the elderly alcoholics causing difficulty in clinical recognition of substance abuse, and furthermore this is compounded by a greater level of co-morbidity and medical, psychiatric and social dysfunction [15].

The Alcohol Use Disorders Identification Test was developed by the WHO in 1982 [17] as a simple way to screen and identify people at risk of developing alcohol problems [18].

Multiple Choice Questions

1. The following are true in relation to alcohol in the elderly, EXCEPT:
   A. The baby boomers are more likely to have been exposed to drug and alcohol.
   B. The 'late onset' tend to be highly educated.
   C. A stressful life event frequently predisposes or exacerbates drinking.
   D. Men are more prone to late-onset alcoholism than women.

2. The following are true of alcohol metabolism and ageing, EXCEPT:
   A. Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) are two enzymes involved in ethanol metabolism.
   B. With ageing there is a decrease in gastric ADH resulting in an increase in the load to the liver.
   C. In the elderly each drink will cause a higher blood level because of the decrease in lean body mass as one ages.
   D. The liver however is able to metabolize the extra alcohol and keep the blood level normal.
3. The following are true of alcohol withdrawal, EXCEPT:
   A. For simple alcohol withdrawal, benzodiazepines are the mainstay of treatment.
   B. If delirium does not resolve in 12–24 h, an alternate diagnosis must be thought of.
   C. Concomitantly the patient should receive vitamins especially thiamine.
   D. Disulfiram (Antabuse) is strongly recommended for use in the elderly.
4. The following are true of neurological complications of chronic alcohol toxicity, EXCEPT:
   A. Wernicke's syndrome is characterized by confusion, ataxia and ophthalmoplegia.
   B. Wernicke's syndrome resembles the manifestations of acute alcoholic intoxication.
   C. 80% of the patients with chronic Korsakoff's psychosis recover fully.
   D. Korsakoff's psychosis is characterized by persistent learning and memory deficits and confabulation.
5. The following are true of Wernicke's ataxia, EXCEPT:
   A. Diplopia
   B. Peripheral neuropathy
   C. Dysphagia
   D. Confusion

MCQ Answers

1=D; 2=D; 3=D; 4=C; 5=C

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Part XVII

Cerebrovascular Diseases in the Elderly

The growing number of older people is at high risk of stroke and stroke incidence rises with increasing age. According to the World Health Organization, stroke is the most common severe neurological disorder and the third leading cause of mortality in adults and the leading cause of mortality and morbidity in the elderly. Epidemiologic and demographic trends of populations particularly in developing countries suggest the burden of stroke is set to rise over the coming decades. Stroke in the elderly will be in the near future a major health issue with significant cost implications as those who are disabled will require a variety of health care and assistance. Several studies have shown different risk profiles between the elderly and younger patients, and the usual vascular risk factors lose their predictive usefulness as age advances. The economic burden is likely to increase with the increase in the number of elderly people in the population. It is the leading cause of debility, and one half of elderly stroke patient suffer permanent loss of function. Part XVII reviews the epidemiology, pathophysiology of stroke, the clinical expression, diagnosis and management, transient ischemic attack, prevention of stroke, and carotid artery disease.

Stroke in the Elderly

77

Contents

Abstract

The growing number of older people is at high risk of stroke. Stroke incidence rises with increasing age and in the very old. Several studies have suggested geographical disparities and regional differences. Several studies have shown different risk profiles between the elderly and younger patients. About 50% of the

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_77

ischaemic strokes are due to atherosclerosis in the large arteries and may follow hypoperfusion or atherogenic embolism. Small vessel disease giving rise to lacunar infarcts amounts to 25%. A further 25% are due to cardiac embolism and the remaining to a number of causes, namely, cryptogenic, arteritis and dissection among others. This chapter reviews the epidemiology and pathophysiology of stroke, its clinical expression diagnosis and management.

Keywords

Stroke · Atherosclerosis · Embolism · Cerebral infarction · Cerebral haemorrhage

Introduction

With an increase in life expectancy and increase in the ageing population in the industrialised nations of the world, the oldest old are the fast-growing segment of the elderly population [1]. The growing number of older people is at high risk of stroke [2]. Stroke incidence rises with increasing age and in the very old [3]. A study of self-reported prevalence of stroke showed 2.5% in those aged 55–64 years, 5% in the 65–74 years, 8.9% in the 75–84 years and 11.6% in the over 85 years [4]. Another study revealed the prevalence of stroke at 85 years to be 18.8%, and the incidence between 85 and 88 years was 52.2/1000 person-years [5]. About half of all strokes occur in the group aged >70 years, and nearly a quarter occur in those who are >85 years of age [6, 7]. The incidence rates of first-ever stroke rose markedly with age and will keep increasing even at 90 years and over, and the percentage of women was higher in patients aged 85 and over [8]. The incidence of all strokes doubles with each decade after the age of 55 years.

Several studies have suggested geographical disparities and regional differences. Comparisons of stroke incidence within countries and communities and between countries are useful to identify high-risk populations. In the United States, the stroke incidence was highest in the southeastern states ('stroke belt') compared to the southwestern and highly populated north-eastern states [9]. Caucasians have a higher rate of coronary artery disease (CAD) and lower prevalence of stroke as compared with Asians [10].

According to the World Health Organisation, stroke is the most common severe neurological disorder and the third leading cause of mortality in adults [11] and the leading cause of mortality and morbidity in the elderly. About 90% of all stroke cases are in people who are 55 years or older, and the death rate doubles every 10 years between 55 and 85 [12]. Although the mortality had been reduced over the last 10 years, yet it still approximates 20–30% within 3 months [13]. Stroke mortality varies considerably by race and sex and there are geographic differences. More recently the large Atherosclerosis Risk in Communities (ARIC) Study showed the occurrence of premature ventricular complexes was associated with new-onset atrial fibrillation and death [14]. Atrial fibrillation (AF) is a relatively common arrhythmia.

There have been several reports [15–17] of a link between socio-economic differences and stroke risk in the elderly. Besides environmental factors for stroke, there is a genetic component. Family history of stroke is known to be an independent risk factor for stroke. Family members have a genetic tendency for stroke, and genetic markers may be of interest in helping to understand the factors that influence the predisposition to stroke. High von Willebrand factor (vWF) levels increased the risk of first ischaemic stroke [18]. vWF plays an important role in platelet adhesion to the subendothelial structures and a useful marker of endothelial dysfunction [19]. Stroke is a leading cause of morbidity and mortality in Western countries [20].

Several studies have shown different risk profiles between the elderly and younger patients [21, 22], and the usual vascular risk factors lose their predictive usefulness as age advances [23, 24]. Atrial fibrillation [8, 25], cognitive impairment [2], congestive heart disease [8] and large artery atherosclerosis [25] are more common in patients older than 85 years, while arterial hypertension [25], diabetes, smoking and hyperlipidaemia have lower prevalence [8, 25] The

Framingham Stroke Risk Score made up of conventional vascular risk factors did not predict risk of stroke in the very old [2].

There is an increase in mortality from stroke in the old old and oldest old [26–28], and age is a strong predictor of stroke mortality [29–31]. Several studies have drawn attention to the protective ischaemic preconditioning-like effect, and TIA may be neuroprotective against ischaemic stroke [32]. The neuroprotective effect of preconditioning involves postischaemic inflammation and [33] has shown that in adult rats subjected to TIA, the prevention of inflammation might contribute by preconditioning-induced protection against focal ischaemia. Most evidence of cellular inflammatory response in stroke is provided by animal models of focal ischaemia induced by middle cerebral artery occlusion [34]. During the acute phase after stroke, there is an increased expression of inflammatory genes including cytokines, chemokines, post-inflammatory transcription factors and adhesion molecules [33] and increase in inflammatory markers such as C-reactive protein [34]. This protective cerebral ischaemic preconditioning effect may be reduced or non-functional in the elderly and may be the cause in part for the higher mortality seen in elderly patients [32].

Approximately 15% of strokes are due to primary intracerebral haemorrhage and the remaining 80–85% to cerebral infarction. About 50% of the ischaemic strokes are due to atherosclerosis in the large arteries [25] and may follow hypoperfusion or atherogenic embolism. Small vessel disease giving rise to lacunar infarcts amounts to 25%. A further 25% are due to cardiac embolism and the remaining to a number of causes, namely, cryptogenic, arteritis and dissection among others.

In cerebral infarction, the mechanisms are:

(i) Embolism – the embolic material originating from the heart (cardioembolic) or from non-cardiac source, for instance, the carotid arteries (artery-to-artery embolism). Cardiac embolism occurs in about 14–30% of ischaemic strokes [35–38]. It increases with age from 14.6% in the group under 65 years to 36% in the very elderly, over the age of 85 years [38].

(ii) Thrombosis – formation of a thrombus or clot within a cerebral vessel. Large artery ischaemic stroke increases from about 30% in the <85 years to 50% in the >85 years [25].

(iii) Haemodynamic – hypoperfusion giving rise to border-zone/watershed infarction. Watershed infarction occurs in about 10% of all ischaemic infarcts and 40% of them occur with carotid artery stenosis [39]. The pathophysiology of watershed infarction is unclear, but it is generally accepted that it results from decreased perfusion in the distal regions of the vascular territories [40].

Within an hour of the ischaemic insult, there is an area of severe ischaemia known as the ‘core zone’ where the CBF is 10–25% of the normal. There is necrosis of the neurons as well as the supporting glial cells. Surrounding this area is an ischaemic zone of oligaemia called the ‘penumbra’. Changes that may occur following cellular injury during the ischaemia and postischaemic reperfusion result in alteration of the blood-brain barrier leading to formation of cytotoxic oedema, vasogenic oedema [41] and haemorrhagic conversion [42]. Cytotoxic oedema occurs within minutes to hours and may be reversible. Hypoxia resulting from acute cerebral ischaemia causes the neurons, glia and endothelial cells to swell due to altering membrane ionic pump function [43]. Ischaemia resulting from impaired cerebral blood flow leads to impairment of ATP synthesis leading to insufficient Na+/K+ ATPase formation [44]. The rapid accumulation of sodium within the cells results in flow of water to maintain osmotic equilibrium causing swelling of all the cellular elements of the brain [42]. In cytotoxic oedema there is no leakage of proteins or extravasation of BBB indicators [45]. Oxidative and inflammatory cascades are initiated early resulting in disruption of the blood-brain barrier, vasogenic oedema and haemorrhagic transformation [43]. Blood-brain barrier disruption results from degradation of endothelial cell activation and endothelial basal membrane by matrix metalloproteinases [43]. The

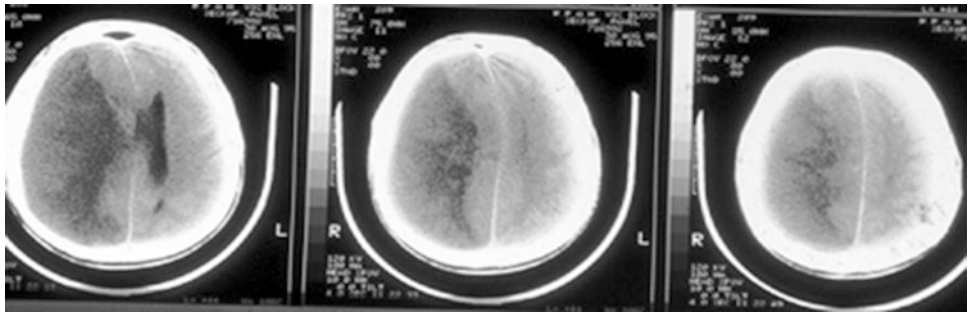

Fig. 1 Shows infarction in the territory of the middle cerebral artery, clearly defined brain oedema and mass effect in the acute phase

vasogenic oedema which is due to defects in the blood-brain barrier [44] occurs over hours to days and is considered to be irreversible. It is characterised by increase in the extracellular fluid volume due to increased permeability of the capillary endothelial cells to macromolecular serum proteins like albumin giving rise to plasma protein containing fluid leaking into the extracellular space. It can give rise to midline shift and to cerebral herniation (Fig. 1). Cytotoxic oedema involves either the grey or white matter. Vasogenic oedema however involves especially the white matter [45]. The larger the infarct, the greater the potential to develop cerebral oedema.

An ischaemic infarct can undergo haemorrhagic conversion or transformation. Haemorrhagic conversion can take two forms, haemorrhagic infarction (HI) or less commonly parenchymatous haematoma (PH). It has been suggested that haemorrhagic conversion may represent an end stage in the course which begins at the outset as oedema [42]. Some haemorrhagic transformation may of indeterminate form with features of both HI and PH. HI is confined within the vascular territory, is asymptomatic and on CT scan appears as hyperdense areas ranging from a few petechiae and patchy to confluent areas of bleeding. PH differs from HI in that it extends beyond the vascular territory, is symptomatic, often exerts mass effect and on CT appears as hyperdense homogenous collection of blood. In most instances PH is due to rupture of an ischaemic vessel which has been subject to reperfusion pressures.

Approximately 80% of primary intracerebral haemorrhages (PICH) are due to hypertensive arteriosclerosis and cerebral amyloid angiopathy [46]. PICH accounts for approximately 10% of all strokes in the United Kingdom [47] and its incidence increases with age [48]. The second most common cause is cerebral amyloid angiopathy. Secondary intracerebral haemorrhages are due to either congenital causes or acquired conditions such as vascular anomalies, coagulopathies, conversion of an ischaemic stroke [49] and various drugs among others. Haemorrhagic conversion following embolic ischaemic strokes can occur without significant mass effect [50] (Fig. 2).

Approximately 30% of all brains removed at autopsy had some degree of CAA in patients aged 60–97 years [51]. In another study 33% of 60–70 years old showed evidence of CAA, and this increased to 75% in those older than 90 years [52]. CAA-related intracerebral haemorrhage is usually larger and the patient much older [53] (Box 1).

Box 1 Key Points. Epidemiology and Pathophysiology of Stroke

Stroke incidence rises with increasing age and in the very old [3].

Several studies have shown different risk profiles between the elderly and younger patients [21, 22], and the usual vascular risk factors lose their predictive usefulness as age advances [4, 23].

(*continued*)

Box 1 Key Points. Epidemiology and Pathophysiology of Stroke (continued)

Atrial fibrillation [5, 8, 24], cognitive impairment [2], congestive heart disease [8] and large artery atherosclerosis [25] are more common in patients older than 85 years, while arterial hypertension [25], diabetes, smoking and hyperlipidaemia have lower prevalence [8, 25].

About 50% of the ischaemic strokes are due to atherosclerosis in the large arteries in over 85 years [25] and may follow hypoperfusion or atherogenic embolism.

Clinical Manifestations

Cerebral Infarction

Cerebral infarction can be classified into lacunar, territorial and watershed infarctions. The territorial infarction in turn is subdivided into cortical and subcortical. Figure 3 shows the blood supply to the brain. Figure 4 shows the cortical and subcortical territories supplied by the main arteries and their main branches.

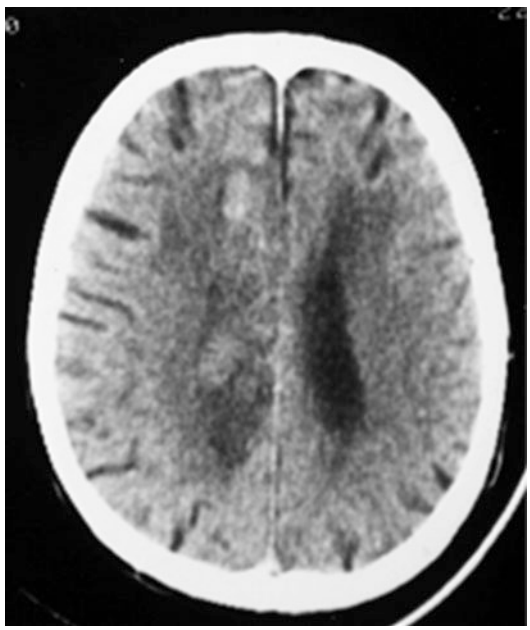

Fig. 2 CT scan showing haemorrhagic conversion

Lacunar Infarction

Lacunar stroke accounts for about 25% of all ischaemic strokes [54–56]. The common lacunar sites are the lenticular nuclei (65%), pons (34%), thalamus (32%) and internal capsule (posterior limb and corona radiata) (27%) [57]. Five classic syndromes, namely, pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis and dysarthria-clumsy hand syndrome, have been recognised [58–61]. The corona radiata, pons and medullary pyramid are the located sites for pure motor hemiparesis. The usual presentations are stuttering symptoms, dysarthria and paralysis of the face, arm and leg [62]. About 85% of pure motor hemiparesis is caused by lacunar infarct [62]. Another cause of pure motor paresis is subdural haematoma. And the prognosis depends on the severity. Pure sensory stroke occurs in lesions in the thalamus and rarely in the internal capsule, corona radiata, pons and brainstem. Symptoms are persistent or and include alter transient numbness and hemianaesthesia. The sensory symptoms usually subside, and in some central post-stroke, pain occurs [58, 59]. Mixed sensory stroke results from lesions in the thalamus, internal capsule, caudate and lateral pons. The corona radiata, thalamus, internal capsule, lentiform nucleus and pons are the common sites for ataxic hemiparesis. Crural paresis, homolateral ataxia and incoordination out of proportion to the weakness occur. The weakness generally improves but the ataxia may persist [60]. The common sites for dysarthria-clumsy hand syndrome are the corona radiata, upper paramedian part of pons and anterior limb of internal capsule. There are facial weakness, dysphagia with mild weakness and clumsiness of the hand. The prognosis is generally favourable [61]. The proposed mechanisms for lacunar infarction include lipohyalinosis, microatheroma, vasospasm, reduced blood flow and endothelial dysfunction.

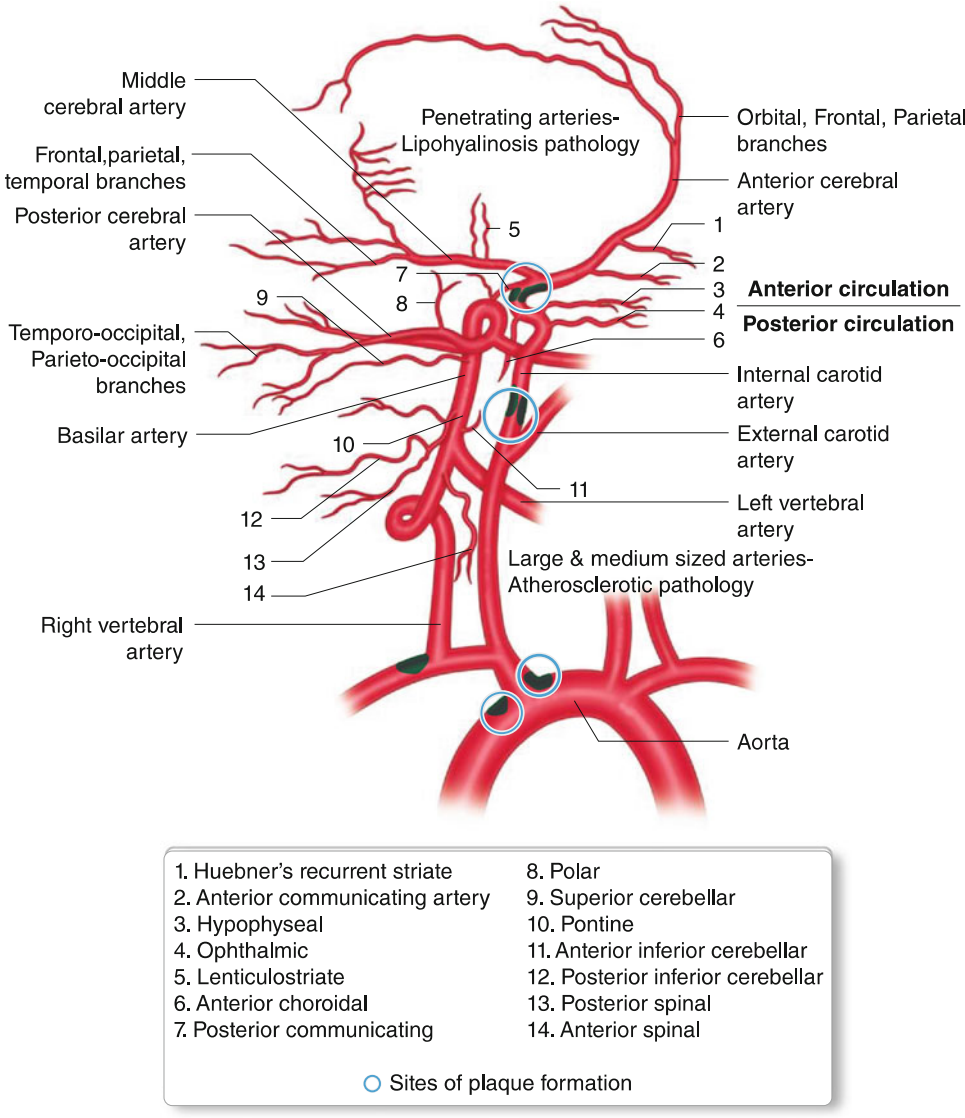

Fig. 3 Scheme of the arterial supply of the brain and the pathophysiology of cerebral infarction

Territorial Infarction

Territorial infarction can be cortical or subcortical. Cortical territorial infarction involves the superficial vascular territory of the main cerebral arteries, namely, anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA) (Fig. 5). Subcortical territorial infarcts occur in the internal border zones between ACA, MCA and PCA and the areas supplied by lenticulostriate, anterior choroidal and the Huebner (medial striate) arteries. The mechanisms include large artery atherosclerosis (artery-to-artery embolism), low flow and cardioembolism. Large artery embolism accounts for about 30% of all ischaemic strokes, and cardioembolic stroke accounts for 14–30% of all ischaemic strokes [63–65]. The potential cardioembolic sources with a high risk are atrial fibrillation, infective endocarditis, myxoma, rheumatic mitral stenosis and regurgitation and prosthetic valves [54].

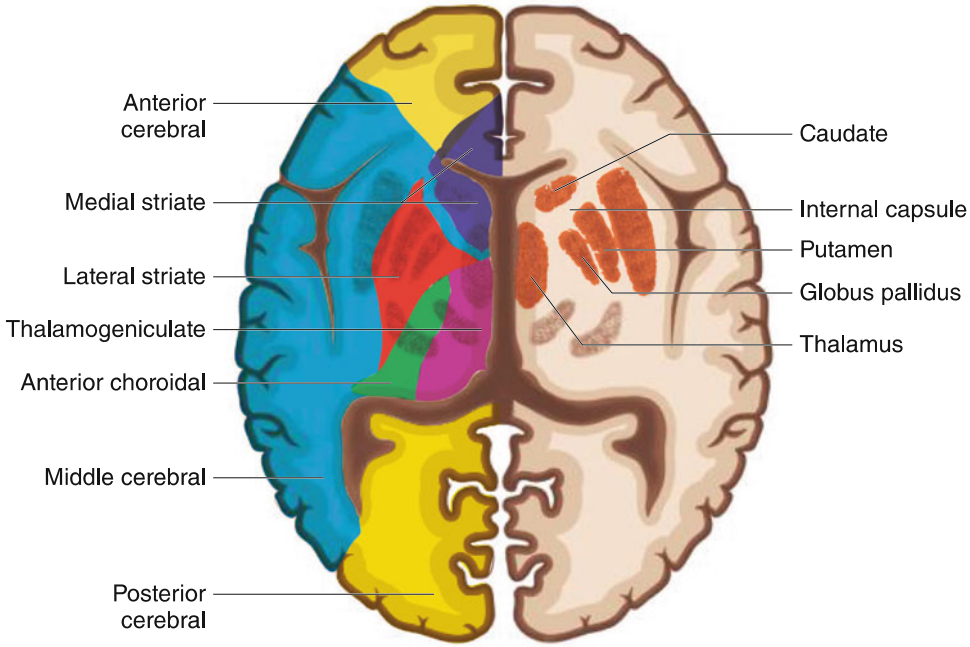

Fig. 4 Schematic diagram of horizontal section of the brain showing the territories supplied by the main arteries, the anterior, middle and posterior, and that supplied by their main branches, the medial striate, lateral striate, thalamo-cortical and anterior cerebral arteries

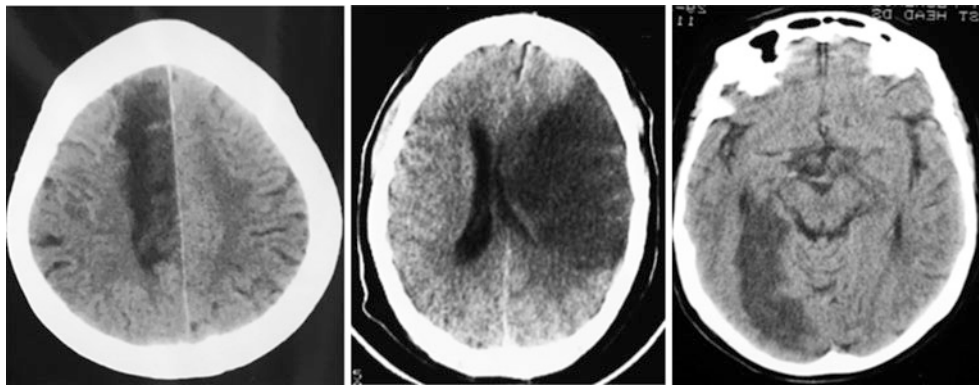

Fig. 5 Shows infarction in the territories of the anterior, middle and posterior cerebral arteries

Anterior Circulation

Infarction in the Territory of the Anterior Cerebral Artery (ACA)

Territorial Infarction: Cortical

Infarction in the territory of the ACA accounts for 0.63% [66, 67], 1.3% [68] and 1. 8% [69] of all ischaemic strokes. The rarity of the ACA infarction is attributable to the distinctive features of the haemodynamics of the anatomy of the arterial tree [66]. A number of mechanisms are involved: (i) artery-to-artery embolism from cardioembolic ICA occlusion [66, 67], (ii) isolated ACA dissection [67], (iii) propagation of thrombus from an occluded ICA and (iv) atheromatous changes with secondary thrombosis [66]. The assumed causes of ACA infarction are large vessel disease

and embolism (cardiogenic and ICA-ACA embolism). Atherosclerosis is the most important actor in stroke aetiology although others have found cardioembolism to be more important [69].

Clinical Features

ACA infarction is associated with several clinical features which are more frequent than that seen in patients with MCA and PCA infarctions. Based on clinico-radiological analysis [68], three clinical patterns depending on the side of the lesion have been described. Those with left-sided infarction had mutism, transcortical motor aphasia and hemiparesis with left leg predominance. Those with right-sided lesion had acute confusional state, motor hemineglect and hemiparesis, and those with bilateral involvement presented with akinetic mutism and severe speech dysfunction. According to them ACA infarction may have similar features to MCA infarction, but callosal syndromes and frontal dysfunction may help in the differential diagnosis.

Territorial Infarction: Subcortical

i. *Infarction in the territory of the anterior choroidal artery* (AChA) is uncommon. The AChA territory lies between the striatum laterally and the thalamus posteromedially [70]. It supplies the lateral thalamus and posterior limb of the internal capsule. Cardioembolism is one of the major causes of anterior choroidal territory infarcts [71]. The syndrome combines the triad of hemiplegia, hemianaesthesia and hemianopia on the contralateral side of the lesion [72–74]. Incomplete forms are much more common [72]. Pathological crying is not a well-accepted manifestation of anterior choroidal artery infarction, but it has been reported in this setting [75, 76].

ii. In 90% of the cases, *the recurrent artery of Heubner* arises from A2 segment of the anterior cerebral artery. It supplies the anteroinferior portion of the internal capsule and anteromedial part of the head of caudate. Infarction involving the artery can be silent. The clinical manifestations include weakness of the contralateral arm and face, dysarthria and hemichorea. Bilateral involvement manifests as akinetic mutism [77].

Infarction in the Territory of the Middle Cerebral Artery

Territorial Infarction: Cortical

MCA infarction increases with age with the highest incidence in the seventh and eighth decades of life [78]. The frequency is reported to be more than 80 per 100,000 [79]. Usually occlusion is embolic in nature, and thrombotic occlusion of the large and small vessels is widely accepted as primary aetiology in general.

Occlusion at the segment M1 in the left dominant hemisphere will give rise to contralateral hemiplegia affecting the face, arm and leg, hemisensory loss, homonymous hemianopia and global aphasia, and these include aphasia, alexia, agraphia and acalculia [80]. The signs and symptoms of right hemispheric stroke include visuospatial perceptual deficits and subtle communication problems.

Middle Cerebral Artery: Subcortical

Striatocapsular infarction – Infarction in the territories of the lenticulostriate arteries (striatocapsular infarction). Affected structures include the anterior limb of the internal capsule, the head of caudate and the putamen. Striatocapsular infarction is known to have variable neurological manifestations including cortical symptoms. The most common clinical presentation is involvement of the upper limb with cortical symptoms such as dysphasia, neglect or dyspraxia [81] (Box 2).

Box 2 Key Points. Clinical Syndromes: Anterior Circulation

Cerebral infarction can be categorised as lacunar, territorial (cortical, subcortical) and watershed (cortical, internal) infarctions.

Five classic lacunar syndromes include pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis and dysarthria-clumsy hand syndrome [58–61].

Clinical manifestations of ACA territory infarction include contralateral sensorimotor deficits mainly affecting the lower limbs.

(*continued*)

Box 2 Key Points. Clinical Syndromes: Anterior Circulation (continued)

Middle cerebral artery territory infarction manifests as contralateral hemiplegia, hemianopia, hemianaesthesia, dominant hemisphere aphasia and non-dominant – apraxia and agnosia [80].

Watershed Infarctions

Watershed infarctions occur in the distal fields of two non-anastomosing arterial systems [82] that is the areas between the cortical supply of the ACA, MCA and PCA (cortical watershed infarction) and the more rostral periventricular and supraventricular white matter of the corona radiata and the centrum semiovale (inner watershed) [83]. The corona radiata is the watershed area between deep and superficial arterial systems of the MCA and the centrum semiovale with the watershed zone between superficial system of the MCA and ACA [83]. Together they are called 'terminal supply infarcts' or 'inner or subcortical watershed infarcts'. The cortical watershed infarction is characterised by infarction in which the border between the two main cerebral arteries divides the infarct into two approximately equal parts [84, 85]. Inner watershed infarcts involve the vascular inner border zone where the infarct is divided equally by the border between the deep and superficial perforating arteries [85–87]. Inner watershed infarcts can be further divided on their radiological appearances into confluent (large single cigar-shaped infarct alongside the lateral ventricle) and partial ('chain-like' or 'rosary') [82].

Posterior Circulation

Territorial Infarction: Cortical

Infarction in the Territory of the Posterior Cerebral Artery (PCA)

Approximately 13% of all cerebral infarcts occur in the territory of the posterior cerebral artery (PCA) [88]. A number of clinical syndromes have been described with PCA infarction depending on the extent of the lesion and location. Depending on the extent of the involvement of the PCA and its branches, the lesions could be located in the inferolateral thalamic territory and paramedian thalamic territory, in other midbrain or thalamic territories or in combinations. Distally it supplies the medial inferior temporal lobe, parahippocampal and hippocampal gyri, and the occipital lobe including the calcarine cortex and visual association areas. The infarctions are unilateral, sometimes bilateral, and are commonly caused by embolism either from the heart or from the atheromatous vertebrobasilar arteries. Patients with PCA infarcts can present with a variety of neurological symptoms. They can present in a confusional state, visual disturbances such as vision loss and field deficits, visual hallucinations, visual agnosia and memory loss.

Posterior Cerebral Artery: Subcortical

Thalamus and vascular syndromes of the thalamus. Occlusion of the artery of Percheron results in bilateral thalamic and mesencephalic infarctions. The main symptoms are vertical gaze palsy (65%), memory impairment (58%), confusion (53%) and coma (42%) [89].

Posterior choroidal artery territory infarction. The most common manifestations of lateral posterior choroidal (PChA) territory infarct included homonymous quadrantanopsia with or without hemisensory loss, transcortical aphasia and memory losses. Medial PChA territory is less frequent and eye movement disorders predominate [90].

Thalamogeniculate territory infarction. TGA branches arise in 80% of the hemispheres from P2 segment of the posterior cerebral artery and in 20% from P3 segment [91]. Lesions are located medial to the dorsal third of the posterior limb of the internal capsule. Small lesions affect the lateral thalamus. TGA infarcts manifested as pure sensory stroke, ataxic hemiparesis and more rarely hypaesthetic-ataxic hemiparesis. Other manifestations include sensorimotor and involuntary movements; 19% of their cases developed classical Dejerine-Roussy syndrome [92] (Box 3).

Box 3 Key Points. Clinical Syndromes: Posterior Circulation

A number of clinical syndromes are associated with PCA territory infarction.

With left-sided lesions – hemianopia, alexia and visual agnosia.

Right-sided lesions – hallucinations and illusions.

Bilateral cortical lesions – severe amnesia, bilateral homonymous hemianopia and visual hallucinations.

Anterior syndromes – thalamic sensorimotor with sensory predominating [89].

Midbrain – hemiplegia, vertical gaze palsy, stupor, ataxic tremor, stupor and coma.

The main blood supply to the lateral medullary area is the direct penetrating arteries from the distal vertebral artery. The posterior inferior cerebellar artery supplies the region in less than third of the cases [99].

Basilar and Vertebral Arteries: Brainstem Strokes

Basilar

Brainstem strokes are categorised into a variety of well-defined syndromes according to the vascular territory involved.

(i) *Anterior inferior cerebellar artery* (*AICA*) *territory infarcts.* AICA infarcts are considered rare, and underdiagnosed reports of non-fatal cases are rarer still [93, 94]. In such infarcts brainstem signs predominate. Vertigo, ataxia, ipsilateral facial weakness and deafness are the usual clinical manifestations. Unilateral infarcts limited to the AICA territory are usually caused by the occlusion of the AICA itself. Sudden deafness is one of the manifestations of AICA infarcts [95, 96] and such deafness may be underdiagnosed.

(ii) *Superior cerebellar artery territory stroke* (*SCA*). In a study of 21 patients with SCA infarction, only two had the classical signs of SCA. Dysmetria, dysdiadochokinesis, dysarthria, ataxia and vertigo were the most common findings [97]. The syndrome of SCA is characterised by loss of pain and temperature on the opposite side of the body, Horner's syndrome with ataxia and weakness and tremor of the upper extremity. Palatal myoclonus had been reported [98].

Vertebral

i. *Lateral medullary syndrome* is the most common brainstem stroke. The main blood supply to the lateral medullary area is the direct penetrating arteries from the distal vertebral artery. The posterior inferior cerebellar artery supplies the region in less than third of the cases suggesting that lateral medullary syndrome is only infrequently caused by cerebellar infarction [99]. The patient presents with vertigo, facial pain, nausea, vomiting, headache and imbalance. Signs on the ipsilateral side include loss of sensation to pain and temperature with loss of corneal reflex and facial pain due to involvement of the V nucleus and descending tract. Involvement of the vestibular nucleus causes dizziness and nystagmus. There is inability to stand and walk, swaying and falling with gait ataxia due to involvement of the cerebellum and restiform body. Horner's syndrome is due to involvement of the sympathetic. On the contralateral side, there is loss of pain and temperature on the body due to involvement of the spinothalamic tract. Often the lateral and medial medullary syndromes are combined (Babinski and Nageotte syndrome).

ii. *Medial medullary syndrome* results from involvement of the medullary pyramid which is supplied by the anterior spinal artery. It is characterised by hemiplegia, upper and lower limb, and sparing of the face with loss of position and vibration sense on the contralateral side. This is accompanied by paralysis of the tongue on the ipsilateral side due to involvement of the hypoglossal nucleus or nerve and lateral lemniscus [100]. In about half the number of cases, there is bilateral involvement with flaccid or spastic quadriparesis.

Cerebral Haemorrhage

The clinical manifestations are sudden in onset with headache, nausea, vomiting, disordered sensorium, raised blood pressure and focal neurological deficits [49]. In about half the patients, there is early progression of the neurological deficits with decreasing level of consciousness [49].

Primary Intracerebral Haemorrhage (PICH)

Much of the primary intracerebral haemorrhage (Figs. 6 and 7) is due to hypertension and cerebral amyloid angiopathy. The first signs of intracranial haemorrhage are caused by dysfunction at the site of the bleeding, and the development of neurological signs will very much depend on the location and extent of the lesion. Epileptic seizures can be an early or late complication of intracerebral haemorrhage, and it is much more common with lobar haemorrhage [101] (Fig. 7).

Small primary intracerebral haemorrhage. Most haemorrhagic strokes are associated with hypertension which causes an intracranial small vessel disease known as lipohyalinosis or fibrinoid necrosis. They are common in the middle and early old age. The most common sites of their occurrence are in the brain areas supplied by the deep penetrating arteries such as the basal ganglia (caudate and putamen), thalamus, pons and cerebellum. They often produce lacunar syndromes characterised as motor hemiparesis, sensorimotor stroke, ataxic hemiparesis, dysarthria-clumsy hand syndrome and pure sensory stroke [102].

Lobar Intracerebral Haemorrhage

Intracerebral haemorrhages lobar in location (frontal, parietal and occipital) are designated lobar intracerebral haemorrhages. The incidence increases with age and is the most common cause of ICH in persons 70 years and older [103]. Such patients do not have hypertension [104]. However some investigators have found pre-existing hypertension in 31–55% of patients [105, 106], and hypertension is common in primary lobar haemorrhages as in deep pontine and cerebellar haemorrhages [107]. Furthermore they felt that hypertension is as important in the development of lobar haemorrhages as amyloid angiopathy. Cerebral amyloid angiopathy has been regarded as a frequent cause of lobar intracerebral haemorrhages [108].

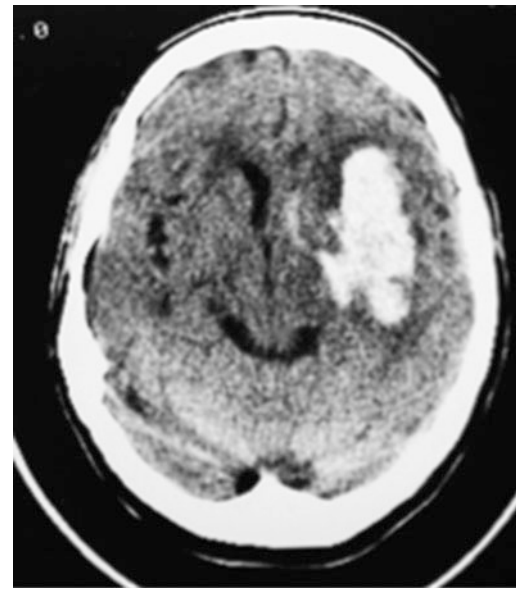

Fig. 6 CT scan showing acute intra-cerebral haemorrhage

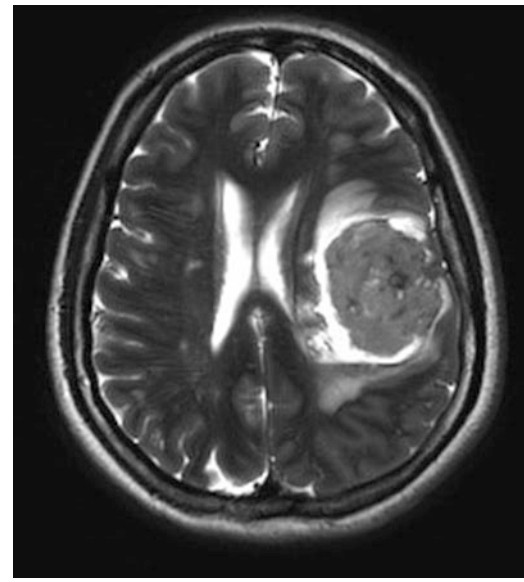

Fig. 7 MRI-axial T2-weighted sequence – acute intracerebral haemorrhage

The symptoms and signs of lobar haemorrhages will depend on the location. In frontal haemorrhages there is weakness of contralateral side, arm more than leg, accompanied by frontal headache. In the parietal, there is hemisensory deficit with headache 'temple' region. Occipital haemorrhage is characterised by ipsilateral eye pain and dense hemianopia. There is fluent dysphasia and poor auditory comprehension in temporal haemorrhage together with pain in the anterior ear [106].

The clinical diagnosis of cerebral amyloid angiopathy (CAA) can be challenging [109], and it is difficult to distinguish from other causes of lobar haemorrhage [107]. Diagnosis during life is impeded by the need for post-mortem examination for definite diagnosis. Using a combination of clinical, radiological and pathological data, the Boston Criteria were developed which aided and reliably differentiated lobar intracerebral haemorrhage into categories of possible, probable or definite based on the likelihood of underlying CAA [110].

Subarachnoid Haemorrhage (SAH)

SAH is often caused by bleeding from either an aneurysm (referred as berry or congenital) or vascular malformation. The aneurysms usually occur at the branching sites of the larger arteries of the circle of Willis. The blood from the ruptured aneurysm spreads through the cerebrospinal fluid around the brain and the spinal cord (Fig. 8). Vascular malformations usually bleed into the brain and/or subarachnoid spaces.

Headache occurs in about two-thirds of the patients and is due to the sudden increase in the intracranial pressure. The headache is sudden, extremely severe reaching a maximum in a few seconds, diffuse and poorly localised and could last for a few minutes to hours to weeks. If bleeding is severe, death can occur. Altered level of consciousness from drowsiness to loss of consciousness, confusion, restlessness, nausea, vomiting and neck stiffness are seen initially followed by stiffness of the back and legs with photophobia few hours later.

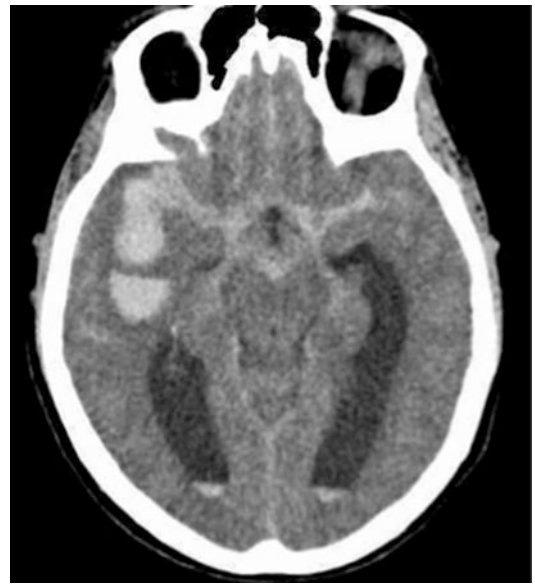

Fig. 8 Image showing subarachnoid haemorrhage following rupture of aneurysm

The spread of the blood in the subarachnoid spaces could affect the cranial nerves (cranial nerves III, VI, IX–XII) and adjacent brain structures (hemiparesis, paraparesis and cerebellar signs), the findings depending on the aneurysm characteristics. Distinguishing syndromes are associated with the different aneurismal locations. Other signs could include subhyaloid haemorrhage and positive Kernig's and Brudzinski's signs. The blood pressure could be raised and there may be fever.

Special Types of Intracerebral Haemorrhage

Putaminal haemorrhage is the most common ICH (Fig. 9). It could present with a wide spectrum of clinical manifestations such as transient neurological deficits [111], pure motor hemiparesis [112], dysarthria-clumsy hand syndrome, ataxic hemiparesis [102, 113] with varying levels of consciousness, neurological deficits, recovery or death. It is usually abrupt in onset with gradual worsening. Global aphasia occurs with a lesion in the dominant hemisphere and hemi-inattention. In large haemorrhages there may be a gaze directed towards the side of the lesion.

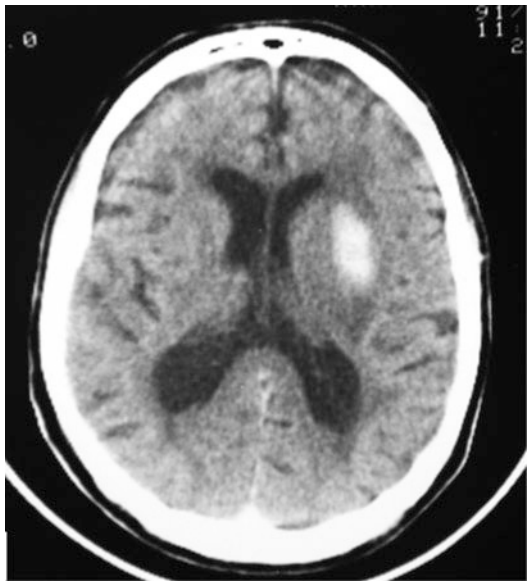

Fig. 9 CT scan shows basal ganglia haemorrhage

Cerebellar haemorrhage. There is a wide spectrum of clinical manifestations from a benign course with little or no deficit to a rapidly fatal case with hydrocephalus and brainstem compression [114]. Nausea, vomiting and vertigo are common symptoms. There is usually a progressive deterioration. About three-quarters of the patients with cerebellar haemorrhage have two of the characteristic triad of ipsilateral horizontal gaze palsy, lower motor neuron seventh cranial palsy and appendicular ataxia [115]. Symptoms usually develop during the day when the patient is active. The common symptom is inability to stand or walk. Headache occurred in 36% and vomiting in 44% in one study although they do not exclude ICH [116].

Pontine haemorrhage (Fig. 10) presents with bilateral signs, quadriplegia, small unreactive pupils, ocular fixation, ocular bobbing, decerebrate posture, respiratory disturbance and eventual demise [114] and almost always arises from the paramedian branch of the basilar artery. It often extends into the fourth ventricle with rapid onset of coma and a high mortality. Patients with hemipontine lesions almost all survive.

Thalamic haemorrhage (Fig. 10) occurs in 10–15% of ICH [117], usually rapid in onset with vomiting, headache and neurobehavioural disturbances. There is usually an impairment of vertical gaze looking downwards with small sluggish or unreactive pupils. Unilateral sensorimotor deficit with sensory signs predominates. There may be transcortical aphasia or apraxia depending on side of haemorrhage.

Caudate haemorrhage occurs in 5–7% of ICH and presents with nausea, vomiting, confusion and disorientation and contralateral hemiparesis and transient hemisensory deficit with a gaze palsy towards the side of the lesion.

Medullary haemorrhage is rare, and the most frequent symptoms at onset are vertigo, dysphagia [114] and sensory symptoms with palatal weakness, nystagmus, cerebellar ataxia, limb weakness and hypoglossal palsy. Less common are Horner's syndrome and facial palsy.

Diagnosis and Management of Stroke in the Elderly

Management of stroke is multidisciplinary and includes several aspects of care. There is considerable evidence to indicate that stroke care units, critical pathways to process rapidly, identification and evaluation of potential stroke patients and multidisciplinary rehabilitation are associated with improved functional outcome. Timely evaluation and diagnosis is foremost because of the narrow therapeutic window in the treatment of acute ischaemic stroke. Initial assessment involves a history, physical examination and thorough neurological and cardiovascular examinations including diagnostic and cardiac tests. In emergency assessment of a patient suspected of stroke, brain imaging is a required component and requisite before any specific therapy [118]. Both CT and MRI are used although CT is available in most institutions and hence remains the most applied brain imaging test.

Neuroimaging in Stroke

According to Rowley [119], imaging of patients with acute stroke should be directed towards assessment of (i) the parenchyma (detection of intracranial haemorrhage), (ii) the pipes

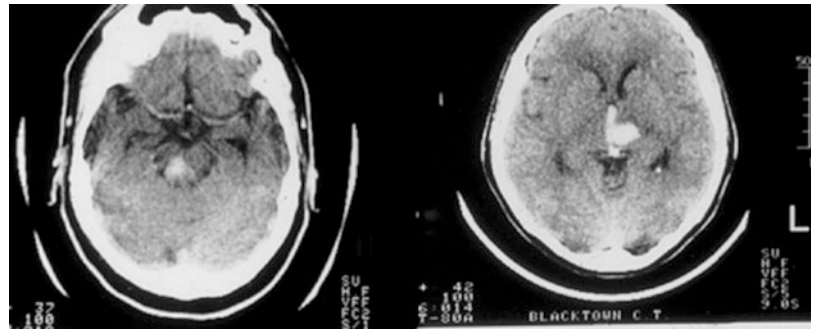

Fig. 10 CT scan shows (i) pontine haemorrhage and (ii) thalamic haemorrhage with bleeding into the third ventricle

(identification of intravascular thrombi) and (iii) perfusion and penumbra (differentiation of infarcted tissue from salvageable tissue). Imaging provides a guide, and this approach facilitates the selection of appropriate therapy and predicts clinical outcome [118]. There is now a need to extend the therapeutic window from 3 to more than 6 h. To do this the following issues have to be addressed, namely, the presence of haemorrhage, treatable intravascular thrombus, size of the core and presence of hypoperfused tissue [120].

Lacunar infarctions are usually not detected by CT scan, and conventional MRI may not identify the acute lacunar infarction related to the clinical symptoms. Small acute lacunar infarcts have been shown to be detected by MR diffusion-weighted imaging (DWI). DWI has demonstrated multiple infarctions in one of every six patients presenting with classic lacunar syndrome [121]. Extracranial atherosclerosis or cardioembolic source has been found with lacunar infarcts although this is more often seen with cortical infarction. These findings highlight the importance of including a carotid ultrasound, echocardiography and cardiac monitoring for atrial fibrillation as part of usual evaluation in patients presenting with a lacunar syndrome (Box 4).

Box 4 Infarction in CT of the Brain and Time

Hyperacute stage: obscuration of the lentiform nucleus with loss of distinction between white and grey matter hyperdense middle cerebral artery sign and hypoattenuation of the insular cortex, 'insular sign'.

Acute stage: clear demarcation, brain oedema and mass effect.

Box 4 Infarction in CT of the Brain and Time (continued)

Subacute stage: brain oedema subsides; haemorrhagic transformation and luxury perfusion may occur. In the second and third week, hypodense to isodense – 'fogging effect'.

Chronic stage: sharply marginated and well-defined ipsilateral ventricle and sulci dilated zone of cystic encephalomalacia and gliosis.

Information references (information sources): Moulin et al. [122], Abdulla et al. [123], Becker et al. [124] and Skriver et al. [125].

Early Intervention

Early diagnosis is followed by early intervention. Several studies have shown the efficacy of admitting stroke patients to specific stroke care units manned by specially trained staff. In stroke the underlying cause can be either a haemorrhage or ischaemia, and hence the management will vary.

Acute Ischaemic Stroke (AIS)

Specific

Thrombolytic Therapy

Ischaemic stroke results from blocking of the artery by a clot and the aim of treatment is to remove the blockage. The clot can either be

broken down (lysis) by pharmacological means or removed by mechanical means (thrombectomy) permitting reperfusion of the ischaemic neurons. Any delay in resumption of blood flow will result in greater damage to the neurons.

Pharmacological thrombolysis involves the use of such agents as tissue plasminogen activator (tPA) or streptokinase. The use of tPA however has been supported by results of randomised controlled trials and meta-analysis. The NINDS clinical trials showed the efficacy of tPA in the treatment of patients with AIS. A more recent study by the European Cooperative Acute Stroke Study (ECASS) in 2008 [126] using alteplase in AIS suggested clinical benefit within 3–4.5 h after the stroke onset. The improved 90-day outcome in patients was comparable to NINDS so were the mortality and cerebral haemorrhage rates, but there were a larger number of large parenchymatous bleeds [126]. One study concluded that rtPA (recombinant tissue plasminogen activator) in patients over 80 years appears to be safe and efficacious [127], and both male and female are equally responsive [128]. Therapy should not be withheld on the basis of age [129]. The reasons for withholding thrombolysis in elderly patients are because of concerns that with advancing age, there is a greater possibility of haemorrhage, poorer prognosis and in-hospital mortality [130, 131]. Compared to the younger patients, patients aged 80 years and over treated with rtPA do not seem to be more prone to ICH [132]. rtPA-treated elderly patients showed improvements both in the acute and in the chronic stage as indicated by sustained improvement in the Barthel Index [127].

Patients who satisfy the inclusion and exclusion criteria are provided with thrombolysis in stroke care units. rtPA is the treatment of choice for patients who present within 3 h of the onset of stroke symptoms. Some of the contraindications to thrombolysis with tPA are severe stroke, seizure at onset, symptoms more than 3 h or time of onset not known, history of prior stroke with concomitant diabetes, prior stroke within the last 3 months, platelet count $<100{,}000$ per mcL, SBP >185 mmHg and DBP >110 mmHG and blood glucose <2.8 or >22 mmol/L [133]. The rate of symptomatic intracerebral haemorrhage in the European Safe Implementation of Thrombolysis in Stroke – Monitoring Study (SITS-MOST) was 7.3% with a calculated mortality rate of 1.9% at 3 months [134]. The Cleveland Study reported intracerebral haemorrhage of 22% [135].

Intraarterial thrombolysis (*IAT*). In intraarterial thrombolysis the thrombolytic is delivered near the occlusive thrombus through a microcatheter and has been found to better the outcome. This has theoretical advantage over intravenous administration and includes local delivery of agent as well as reduced systemic effect and offers a higher recanalisation rate than IV tissue plasminogen activator [136].

Thrombectomy. In patients with a large vessel AIS due to a large clot, it may be less likely to recanalise with the use of tPA. In such situations endovascular mechanical thrombectomy is an option in this subgroup and in those who are unable to receive tPA. High rates of successful recanalisation (57.8%) with fewer periprocedural complications in 6.9% were reported by the Multi MERCI Study [137].

Angioplasty and stenting. The availability of self-expanding intracranial atherosclerotic stents (SEIS) which can be deployed rapidly and safely has made acute stenting an option in treating AIS. A high degree of technical success (97%) and a 4.6% rate of complications were reported by an NH-funded registry [138].

Malignant Middle Cerebral Artery Infarction

Incidence is estimated to be less than 1% of all strokes [139]. Malignant MCA infarction is characterised by a rapid progression of neurological deficits with pronounced space occupying effect resulting in transtentorial herniation [140]. Coma terminates in brain death within 2–5 days of onset [139]. It is one of the most ravaging forms of ischaemic infarct with a mortality of approximately up to 80% with medical treatment [140]. Symptoms such as disordered sensorium together with neurological decline should alert the clinician to this syndrome in a patient with a large MCA infarct and supported by radiological evidence of cerebral oedema and mass effect. Young patients are particularly prone to mass effect unlike the elderly patient

with atrophy that makes them more tolerant to focal infarct-related oedema [139]. Patients with malignant MCA infarction very often have gaze deviation due to involvement of the frontal eye fields together with flaccid hemiplegia [140], hemianaesthesia with global aphasia in dominant hemisphere involvement and severe hemispatial neglect with non-dominant involvement. Hemicraniectomy is thought of as an essential life-saving measure, but there is continuing debate on its appropriateness. The chances of survival may be higher after the operation [141], but mortality and functional outcome are worse in patients especially in those over the age of 60 years [142]. Although observational studies have suggested a reduction in mortality with associated functional gains [143], many clinicians are hesitant to do what they feel or believe is a heroic but potentially a futile procedure except in a few selected patients [144].

General Measures

The physiological parameters such as increase in temperature, hypoxia, blood pressure (hyper-/hypotension), glucose levels (hypo-/hyperglycaemia), hydration/nutrition and cardiac arrhythmias in AIS can exacerbate brain damage and worsen outcome [144]. Control of the physiological parameters such as glucose and blood pressure together with intense monitoring has been cited as one of the benefits of acute stroke unit care. Physiological monitoring is an essential part of acute stroke unit care [144].

Hyperglycaemia after acute stroke is associated with poor outcome. However there is no general agreement as to the optimal method of glycaemic control and how intensely the glucose levels should be lowered avoiding the risks of hypoglycaemia [144]. *Elevated blood pressures* occurred in 80% of the patients with acute stroke on presentation, and approximately 30% had a history of hypertension [145]. Sixty percent of the stroke patients are left normotensive due to spontaneous falls in the blood pressures in 4–10 days [146]. Cerebral blood flow is maintained within normal limits by cerebral autoregulation and becomes impaired after acute stroke. Cerebral blood flow becomes dependent on systemic blood pressure, and any reduction of the systemic blood pressure will reduce the cerebral blood flow to the ischaemic penumbra. Impaired autoregulation occurs in patients with chronic hypertension, and autoregulation occurs at higher blood pressure. This means that antihypertensive therapy may have deleterious effects. The Scandinavian Candesartan Acute Stroke Trial (SCAST) has shown that there is a risk of stroke progression with lowering of blood pressure in the acute phase of stroke [147]. Severe hypertension contributes to brain oedema and increases the risk of haemorrhagic transformation. Patients identified for tPA administration must have their blood pressure elevations treated aggressively and in others with ischaemic stroke for minimising the risk of intracerebral haemorrhage. Two readings should be taken at 5 min apart, and if the systolic blood pressure (SBP) is 130–230 mmHg or diastolic blood pressure (DBP) 105–120 mmHg or SBP >230 mmHg or DBP 120–140 mmHg in a single reading, IV labetalol boluses are employed, and when the DBP is more than 140 mmHg, continuous IV nitroprusside is employed [148]. It is recommended that the temperature be kept normothermic at 36.0–37.0 C. Sustaining nutrition is vital because dehydration or malnutrition will have detrimental effect on stroke recovery.

Stroke patients are prone to develop aspiration pneumonia, hypoventilation, atelectasis and pulmonary embolism and are at risk of hypoxia. Hypoxic patients must be given supplemental oxygen if the oxygen saturation is below 95%. However it should not be given to non-hypoxic patients with mild and moderate stroke [149]. Damage to the cerebral areas results in increased sympathoadrenal tone causing cardiac myocyte damage and repolarising ionic shifts giving rise to ECG repolarisation changes and arrhythmogenesis [150]. It is suggested that patients with acute stroke should have cardiac monitoring for 3 days following the event. Those with ECG evidence of ventricular repolarisation should have continued monitoring till it is resolved. These patients are at risk of sudden death or stroke extension due to cardiac arrhythmias [151].

Intracerebral Haemorrhage (ICH)

In intracerebral haemorrhage therapy is largely supportive. It carries a high mortality with a 30-day mortality of approximately 40% [48]. There are many factors that influence the management of ICH, such as haematoma growth, oedema, blood pressure and cerebral perfusion, other factors being acute hypoxia, fever and increased intracranial pressure among others. Early haematoma growth occurs in 18–38% of the patients within 3 h of ICH onset [152]. The haematoma volume at presentation with further increase in the volume and development of intraventricular haemorrhage have been shown to be independent predictors of poor outcome, and hence early restriction of intracerebral haemorrhage is of paramount importance. In selected patients early treatment with IV haemostasis and minimally invasive surgery may improve mortality and outcome [153]. Recombinant activated factor VII (rFVII) has been tried to reduce the haematoma growth after ICH. It was reported that treatment with rFVII within 4 h of the onset limited haematoma growth and improved functional outcome at 90 days. A small phase II trial evaluated a wide range of doses of rFVII found there were no safety concerns [154]. A further study in an international phase III trial is underway.

The American Heart Association and the American Stroke Association have set out evidence-based guidelines for treatment of spontaneous intracerebral haemorrhage in adults [155]. Ideally the patient should be in the intensive care unit for monitoring and treatment. Initial treatment includes control of blood pressure (more aggressively compared to patients with ischaemic stroke) bearing in mind that over-aggressive treatment of the blood pressure may decrease cerebral blood flow and increase brain damage [156, 157]. Increased intracranial pressure is controlled by osmotherapy, controlled hyperventilation and barbiturate coma and ventricular drains in those with or at risk of hydrocephalus [157]. Prophylactic antiepileptic therapy for patients with ICH may be considered for 1 month [40]. Patients with cerebellar haemorrhage who show neurological deterioration or have brainstem compression and/or hydrocephalus will require surgical evacuation as soon as possible [158] (Box 5).

Box 5 Key Points. Diagnosis and Management of Stroke

The primary care physician should recognise the signs and symptoms of stroke, expedite transportation to the correct hospital and early notify the receiving hospital. In emergency assessment of a patient suspected of stroke, brain imaging is a required component and requisite before any specific therapy [118].

According to Rowley [119], imaging of patients with acute stroke should be directed towards assessment of (i) the parenchyma (detection of intracranial haemorrhage), (ii) the pipes (identification of intravascular thrombi) and (iii) perfusion and penumbra (differentiation of infarcted tissue from salvageable tissue).

rtPA (recombinant tissue plasminogen activator) in patients over 80 years appears to be safe and efficacious [127].

Patients who satisfy the inclusion and exclusion criteria are provided with thrombolysis in stroke care units.

Therapy should not be withheld on the basis of age [129].

Patient with stroke symptoms and after excluding haemorrhage by CT or MRI should be given aspirin 150–300 mg daily as soon as possible.

Physiological monitoring is an essential part of acute stroke unit care [144]. The stroke patient must be closely monitored for neurological and medical complications.

Subarachnoid Haemorrhage

Investigations: CT scan is positive in 85% when performed within 1–2 days. If done early CT is negative, and lumbar puncture should be undertaken to look for xanthochromia and is done at least 12 h after the onset of the headache (to distinguish from traumatic tap).

Treatment: If no clipping or coiling is done, 10% rebleed within hours, 30% few hours to weeks and 2–3% in a year. Delayed cerebral ischaemia indicates a bad prognosis (usually occurs 4–14 days after the onset) due to vasospasm or structural changes in the wall of one or more cerebral arteries.

Identification of Complications

The stroke patient must be closely monitored for neurological and medical complications. Early and late complications are shown in (Box 6). Prevention of decubitus ulcers begins with a thorough skin evaluation at the time of admission. The risk factors include the dependence in mobility, peripheral vascular disease, diabetes, urinary incontinence and lower body mass index [155]. After stroke constipation and faecal impaction are common.

Box 6 Complications of Stroke: Early and Late

With 2–3 days – cerebral oedema
- Increased intracranial pressure, possible
- Transtentorial herniation and death
- Haemorrhagic transformation and seizures
- Aspiration pneumonia, deep vein thrombosis
- Urinary tract infection, septicaemia

Late complications – decubitus ulcers
- Spasticity, contractures
- Post-stroke depression

Rehabilitation

The practice in stroke care units is to commence rehabilitation from day 1 as soon as the condition is stabilised. Rehabilitation assessments should include evaluation of cognitive and communicative skills, physical functioning and psychosocial history and resources [155]. Several studies have demonstrated the benefits of stroke unit rehabilitation regardless of age and the need for additional therapy in facilitating functional recovery. It is believed that the elderly with stroke will have a poorer outcome compared to the younger stroke patients, and the success rate of stroke rehabilitation is lower in the older patients.

One of the strategies gaining popularity is the establishment of specialised stroke units for stroke rehabilitation. With the creation of specialised stroke rehabilitation units, the benefits of stroke units may be influenced by age and the problems associated with ageing [159]. The extra needs of the elderly are better met in the specialised units rather than in the general ward. Several studies have demonstrated the benefits of stroke unit rehabilitation regardless of age and the need for additional therapy in facilitating functional recovery [160]. There are often small variations between young and the elderly groups that can be explained by age alone, but this fact alone should not deny elderly stroke patients to rehabilitation based solely on advanced age.

Brain recovery may take place by several mechanisms. Neuroplasticity refers to the brain's ability to restructure itself and can take various forms. Soon after a stroke, there is initial improvement which lasts for a few weeks and is largely due to the resolution of associated local factors such as oedema, penumbra-ischaemic metabolic injury, diaschisis [161] and blood pressure among others. Another step in the recovery which begins early and can last for several months is neuroplasticity [161] which refers to the brain's ability to restructure itself following task-specific repetitive exercises and workout, making restitution for loss function.

Stroke results in damage to the brain causing a number of deficits in the different neurological domains most commonly to the motor system. Other deficits include sensory disturbances, problems of using or understanding language, cognition, memory and behaviour. Motor defects are the most common impairments after acute stroke and persist in nearly half of all patients [162]. Between one-third and two-thirds of stroke patients lose functional ability in their more affected arm and hand [163]. There are new options, therapy interventions and devices to help stroke patients to regain motor function. Matching specific impairments to different rehabilitation techniques, improvements in arm function were

seen with constraint-induced movement therapy (CIMT), electromyographic biofeedback and robotics [164]. Functional electrical stimulation (FES) has been shown to enhance motor recovery after stroke and can strengthen muscles, increase range of movements, reduce spasticity and prevent contractures.

The management of complications both medical and neurological plays an important role in inpatient stroke rehabilitation [165]. Elderly patients have a high incidence of recurrent stroke together with co-morbidities and have a poorer outcome.

Spasticity, Spasms and Spastic Dystonia

Spasticity is characterised by increased tone, exaggerated reflexes, clonus and muscle spasms resulting from an upper motor neuron lesion. Treatments include stretching, splinting, exercises or surgery for contracture. Consideration should be given to the use of medications such as dantrolene, oral baclofen, tizanidine or botulinum toxin. There is some data as to the usefulness of oral baclofen in stroke [166] but can cause significant sedation and have less impact on stroke-related spasticity [167]. Dantrolene however has restricted trial data to support its use in stroke but has no cognitive side effects [168]. Botulinum toxin injections have been recommended for selected patients with spasticity due to stroke [169, 170].

Shoulder subluxation. Shoulder subluxation after stroke is characterised by partial or incomplete dislocation of the shoulder joint. The shoulder should be kept in the ideal position at all times and movements of the shoulder and upper limb carried out with the utmost care. Treatment entails the use of heat or ice packs, analgesics, support device and strapping of the shoulder (sling). Overhead pulleys should be avoided. Treatments include functional electrical stimulation (FES) early after the onset of stroke [171] and intra-articular injections (triamcinolone) in patients with shoulder pain. Other treatments include hydrotherapy, acupuncture and muscle toning with strengthening exercises and improving range of movements through stretching and mobilisation techniques.

Shoulder-hand syndrome (*SHS*). SHS is characterised by pain and limitation of movement of the shoulder, wrist and hand with swelling followed by atrophy of the muscles and osteoporosis of the underlying bones. Treatment includes medications, physical therapy, psychotherapy, regional anaesthesia and sympathectomy [171].

Post-stroke dystonia. The term 'dystonia' refers to abnormal fluctuations in muscle tone produced by normal patterns of muscle contraction and phasic movements of various types such as tremors and dystonic spasms.

Post-stroke Depression (PSD), Emotionalism and Anxiety

Thirty percent [172] to forty percent [173] of stroke patients develop depression either in the early or late stages after stroke. It is the most common complication stroke survivors experience during inpatient stroke rehabilitation [174]. It is a common complication of stroke and a leading cause of increased mortality and morbidity and can impede rehabilitation process [175]. PSD is associated with a poor prognosis and may hinder recovery. SSRIs such as fluoxetine appear to improve recovery. It is not uncommon to see post-stroke patients exhibiting emotionalism, and about 15% of them show extreme form of emotional change – 'uncontrollable' laughter/crying – and if not treated develop clinical depression [176]. Another psychiatric syndrome is anxiety and co-exists with post-stroke depression and is often undiagnosed [172]. General anxiety disorder accompanying post-stroke depression delays recovery from depression and reduces overall social functioning [177].

Post-stroke Fatigue

Post-stroke fatigue (PSF) is a common sequel to stroke but often is underdiagnosed. It is important to recognise PSF for it can impede recovery and rehabilitation [178] and may have a negative impact on the quality of life and daily functioning [179]. Sleep disorders, sleep-disordered breathing, limited exercise capacity and increased gait energy cost can be related to physical fatigue [180]. It occurs in 30–72% of stroke survivors

[180–182], but few studies have documented its high frequency [177].

There are several impediments such as depression, poor motivation, severe motor deficit, perceptual impairment, poor pre-stroke health, communication disabilities and impaired cognition, factors which may retard recovery. Post-stroke recovery shows differing patterns across varied areas of neurological function. For example, in 95% of the patients, maximum arm motor function is achieved by 9 weeks [183] and in 95% of patients formal level of language function by 6 weeks [166] (Box 7).

Prevention of Recurrent Stroke

The acute hospitalisation is focused not only on treatment of the acute stroke but also in identifying risk factors for recurrent stroke. Post-stroke outpatient care is largely rehabilitation and prevention of recurrent stroke. The risk factors for stroke include hypertension, diabetes, hyperlipidaemia, diabetes and lifestyle factors such as smoking, alcohol abuse, diet and activity.

Box 7 Sequence of Recovery

Level of consciousness improves.

Head and neck control with improved balance sitting up.

Truncal control with balance on standing.

Limb control proximal to distal flaccidity to spasticity.

Functional recovery.

Impact of Stroke

Life expectancy has increased in Europe and many other countries [184], and the proportion of elderly population is increasing [16, 185]. Due to increase in the elderly population, the rates of stroke are expected to increase over the next several decades. The elderly face myriad of problems and challenges, including cognitive impairment, physical disabilities [186], social isolation, financial pressures, co-morbidities and multiple medications. Demographic and epidemiological trends suggest the stroke in the elderly will be a major health issue in the near future with significant cost implications. It is the third leading cause of death in the United States [187, 188], and according to the American Heart/Stroke Association, four million Americans are living with the effects of stroke [188]. In both sexes, age is a stronger predictor of stroke mortality [189–192]. This age-related increase in mortality may be due to age-related changes that occur with ageing such as neuronal loss, altered mitochondrial metabolism and calcium neurotoxicity [193, 194]. Stroke is a damaging affliction that has considerable immediate- and long-term physical, social and emotional dysfunction [195] in the survivors. The economic burden is substantial, and the estimated annual cost for stroke in the United States is approximately $51.2 billion [188] and $73 billion. The economic burden is likely to increase with the increase in the number of elderly people in the population [196]. It is the leading cause of debility [197], and one-half of elderly stroke patient suffer permanent loss of function [198, 199]. The elderly stroke survivors with their multiple disabilities impair outcome and are more likely to need long-term care in aged care facilities. A study of stroke severity in acute stroke and cognitive impairment 18 months after the acute stroke onset was shown to be associated with impairment in activities of daily living and increased costs for utilisation in the first year [196]. Persistent dependency for one or more ADLs by 6 months after strokes was seen in one-fourth and one-third of stroke patients [199, 200] (Box 8).

Box 8 Key Points. Rehabilitation in Stroke

The practice in stroke care units is to commence rehabilitation from day 1 as soon as the condition is stabilised.

A forceful stroke rehabilitation programme is crucial for best functional outcome, and elderly stroke patients should not be denied rehabilitation based solely on age.

(*continued*)

Box 8 Key Points. Rehabilitation in Stroke (continued)

The management of complications both medical and neurological plays an important role in inpatient stroke rehabilitation [165].

After discharge from hospital, the basic issues are secondary prevention strategies and patient adherence to post-stroke rehabilitation guidelines.

There are now new options, therapy, interventions and devices to help stroke patients to regain motor function.

Multiple Choice Questions

1. The following are true in relation to risk factors for stroke, *except*:
   A. Family members have a genetic tendency for stroke.
   B. About 90% of all stroke cases are in people who are over the age of 55 years.
   C. Premature ventricular complexes have been shown to be associated with new-onset AF and death.
   D. High von Willebrand factor (vWF) levels are not associated with increased risk of stroke in the general population.
2. The following are true in relation to anterior circulation syndromes, *except*:
   A. A complete circle of Willis is an anatomical predisposition for little or no neurological deficits in patients with internal carotid artery obstruction.
   B. It is postulated that low flow and emboli co-exist in border-zone infarctions and internal carotid artery disease.
   C. Aphasia occurs in 20% or more in patients after stroke and is the most common language disorder among older people.
   D. About 50% of ischaemic strokes are due to small vessel disease.
3. The following are true, *except*:
   A. Cerebral amyloid angiopathy is common in the elderly and is often associated with Alzheimer's disease.
   B. About 80% of primary cerebral haemorrhage is due to spontaneous rupture of small vessels damaged by hypertension.
   C. The rarity of the anterior cerebral artery territory infarction is attributed to the haemodynamics of the anatomy of the arterial tree.
   D. Anterior cerebral infarction increases with age, and the highest incidence is in the seventh and eight decades of life.
4. In stroke the following are true regarding CT scan of the brain, *except*:
   A. Delineate regions or territories supplied by the major cerebral arteries.
   B. Identify blood clots in the cerebral vessels.
   C. Detect mass effect and brain oedema.
   D. Detect intracerebral haemorrhage.
5. With CT scan of the brain in the current understanding of the mechanism, the following are taken to be embolic, *except*:
   A. Corticocerebral territorial infarction
   B. Red infarct
   C. Capsular infarct
   D. Pontine infarct
6. The more important roles of the CT scan in stroke in the hyperacute stage are true, *except*:
   A. To exclude such conditions as tumours that can mimic stroke
   B. To exclude cerebral haemorrhage
   C. To detect severe mass effect from cerebral oedema
   D. To visualise a hyperdense middle cerebral artery
7. The following in relation to stroke are true, *except*:
   A. Small lacunar infarcts are liable to be asymptomatic.
   B. Haemorrhagic infarction may occur within 24 h of the onset of symptoms.
   C. In hypoperfusion the infarcts are generally in the watershed areas.
   D. Infarction in hypertension occurs in the superficial cortical part of the brain.
8. In stroke the following are true in relation to the vascular territory involved, *except*:
   A. Cortical infarction in the territory of the left middle cerebral artery is characterised by hemiplegia, hemianaesthesia, hemianopia and aphasia.

B. Infarction in the territory of the anterior cerebral artery occurs only in 3% of all strokes.
C. Anterior cerebral artery involves the arm and face and to a lesser degree the foot and leg.
D. The mechanisms for large corticocerebral territorial infarct include large artery atherosclerosis (artery-to-artery embolism), low flow and cardioembolism.

9. The following findings on the CT scan are true, *except*:
A. Severe mass effect indicates poor prognosis.
B. Horizontal pineal deviation of more than 4 mm carries a poor prognosis.
C. Infarction in the left perisylvian area is associated with aphasia.
D. Functional outcome does not relate to the size of the infarction.

MCQ Answers

1 = D; 2 = C; 3=A; 4 = B; 5 = C; 6 = C; 7 = D; 8 = C; 9 = D

Case Study 17. Herpes Zoster and Stroke

Presentation: A 78-year-old man was seen with confusion, anorexia and lethargy of 1 day in duration. He had developed a rash across the left side of his chest the previous day consistent with herpes zoster involving T4 dermatome. Physical examination revealed he was reasonably alert but with reduced attention span. He was disorientated to time and place and this continued to day 3. There were no overt abnormalities in the systems, but neurological examination revealed weakness of the left arm. The gait was normal but tandem was not possible. Routine haematological and biochemical investigations revealed no abnormalities. There was a slight increase in the CSF proteins, with white cells (mainly lymphocytes) increased (21), but gram stain revealed no organisms. The CT scan of the brain revealed no focal abnormalities and a repeat a few days later was the same. The virology of blood showed positive IgG and IgM suggesting recent infection, but unfortunately the CSF had been misplaced. He was treated with acyclovir, and when reviewed 3 weeks later, he had largely recovered.

Comment: We believe in all probability he had a stroke following herpes zoster. Stroke and TIA are recognised complications of herpes zoster [201]. It had been postulated that the pathogenesis of the neurological complications of varicella zoster virus is caused by direct viral invasion [202]. Viral inclusions and antigen in the cerebral arteries at autopsy indicate varicella zoster virus vasculopathy in patients with associated stroke and TIA [203]. Epidemiological studies have shown that zoster virus is a risk factor for stroke, and the risk can be reduced with antiviral therapy [204].

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Transient Ischaemic Attack (TIA) 78

Contents

Abstract

TIA frequency increases with age reaching 10.2% in males and 7.4% in females and decreased in subjects of both sexes aged 85 years or over. The symptoms of TIA vary widely depending on the area of the brain involved. Medical history of specific symptoms and thorough neurological and cardiovascular examinations provide the most important information to diagnose a TIA. TIA poses considerable difficulty in diagnosis, and diagnostic uncertainty is common. Patients presenting with TIA or minor stroke are at high risk of early stroke up to 10% in the first 48 h. Current international guidelines have adopted the ABCD2 score in risk stratification of patients with TIA. For a new-onset TIA patient, an ABCD2 can be a guide in the management.

Keywords

Transient ischaemic attack · Carotid artery stenosis · Embolism · Transient monocular blindness · ABCD2 scores

Introduction

A transient ischaemic attack (TIA) is a circulatory event which produces a focal neurological deficit with complete recovery within 24 h. With the advent of sophisticated neuroimaging techniques, the definition of TIA has unfolded to less than 1 h episode of focal dysfunction with no imaging evidence of acute infarction, according to the TIA Working Group [1]. The American Heart Association and American Stroke Association [2] endorsed this new definition but omitted the phrase 'less than one hour'. The cut-off period of any duration for TIA is incorrect,

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_79

for diffusion-weighted imaging of patients with TIA with symptoms less than 30 min had shown no abnormalities whereas in 29% with TIA lasting for 6–24 h revealed abnormalities [1].

An estimated 32,000 Australians suffer a first-ever stroke each year [3], and a similar number are affected by TIA [4]. The overall prevalence of TIA is 7% in males and 4.9% in females. Their frequency increases with age [5] reaching 10.2% in males and 7.4% in females and decreased in subjects of both sexes aged 85 years or over [6]. TIA was substantially higher among Blacks and women than among Whites and men [7]. Those with TIA and hypertension experienced higher stroke incidence rates, and 13% of those with TIA had evidence of cardiovascular disease [8]. The incidence of cardiovascular disease and mortality is three times higher in the elderly from stroke compared to younger patients [9, 10], and patients over the age of 80 years due to accumulation of vascular risk factors are at increased risk of ischaemic stroke [11].

About 40% of patients with ischaemic stroke syndromes have extracranial arterial lesions accessible to surgery [12] most commonly carotid stenosis [13]. The most common cause is an embolus from the atherosclerotic plaque in one of the carotid arteries or from a thrombus in the heart. Large vessel disease (especially high-grade carotid stenosis) and cardioembolism (atrial fibrillation and severely diseased and replaced valves) carry higher risks of stroke recurrence [12]. In the former, the stroke risk was found to be 12.6% within 1 month and 19.2% at 3 months, and in the latter, it was estimated to be 4.6% within a month [14]. In one-third of the patients with TIA, no further symptoms are experienced, one-third continue to have TIAs, and the remaining one-third have completed strokes [15]. In another study, 10–20% of the patients with TIA had a stroke within 90 days, and in about half of them, the stroke occurred within 24–48 h [16].

Symptomatology

The symptoms of TIA vary widely depending on the area of brain involved. The presentation of TIA symptoms can often be divided according to the vascular territories involved, anterior (carotid) circulation and posterior (vertebrobasilar) circulation. It is important to distinguish between them if carotid endarterectomy is to be considered although the clinical distinction can be difficult. Despite this, there are clinical features that are more likely to be allied to one or the other:

Anterior circulation TIA (carotid TIAs): Transient occlusion of the ophthalmic artery will result in monocular blindness (TMB) or amaurosis fugax and described by the patient as a 'curtain' descending over the affected eye. It may also manifest as a transient hemispheric episode.-weakness, clumsiness of hand, dysphasia and dysarthria.

Posterior circulation TIA: Any one of these symptoms diplopia, dysarthria, ataxia, vertigo, blurred vision and transient global amnesia and may occur as an isolated symptom of posterior circulation involvement but for isolated vertigo without other symptoms is most unlikely to be caused by vertebrobasilar disease.

Differential Diagnosis

There are many non-vascular conditions that may cause symptoms suggestive of TIA or stroke and have often been referred to as 'TIA mimics' or 'stroke mimics' [17]. The most common mimics are hypoglycaemia, migraine, seizures, post-ictal states and tumours. Hypoglycaemia manifests with confusion, visual disturbances and inappropriate behaviour and accompanied by sweating, tremulousness, hunger and diminished level of consciousness or coma [18]. Transient hypoglycaemia may simulate a stroke like event with hemiplegia and aphasia [19]. Hypoglycaemia can be excluded by appropriately timed blood sugar levels. Migraine occurs in young and middle-aged patients and is characterised by headache often unilateral and an aura which precedes the headache. If the patient has not had migraine headaches in the past, this diagnosis should not be made until all other possibilities are excluded [20]. Todd's paralysis is characterised by temporary usually unilateral weakness and may last for 36–48 h following a seizure. There have been reports of stroke and TIA symptoms with chronic subdural haematoma [21]. Transient global

amnesia appears suddenly with confusion, disorientation and lasts as long as 2 h or more together with retrograde memory deficit [20].

In transient monocular blindness (TMB) or amaurosis fugax, the visual disturbance or loss such as blindness, dimming or blurring affects one eye for seconds or minutes [22]. It may occur alone or in combination with TIA. Differential diagnosis of TMB includes ocular events such as vitreous detachment, central retinal vein thrombosis, intraocular haemorrhage, intermittent angle chronic glaucoma and vasospasm/angiospasm [23].

Diagnosis and Evaluation of a Patient with Suspected TIA

Medical history of specific symptoms and thorough neurological and cardiovascular examinations provide the most important information to diagnose a TIA. TIA poses considerable difficulty in diagnosis and diagnostic uncertainty is common. A third of patients referred to a TIA/stroke clinic have a non-vascular cause [24], and only 22% of primary care physicians knew of the definition of TIA [25].

Risk Stratification

Patients presenting with TIA or minor stroke are at high risk of early stroke up to 10% in the first 48 h [26]. The overall risk of stroke in patients with TIA has been found to be 8% within a week and 20% with a 3-month period [27]. There are several scoring systems based on the clinical profile of patients used to determine the risk of early stroke recurrence after a TIA. Presently a validated score – the ABCD2 score – is from five factors with seven points [28]. The risk of stroke within 2 days following TIA with a score between 0–3 is 1%, 4–5 is 4.1% and 6–7 is 8.1%, respectively [28]. Although validated in several studies, the ABCD2 score is not wholly dependable in predicting carotid artery stenosis [29]. The ABCD2 score may act as a guide but what is important is the identification as to the mechanism and pathology of the TIA for these are what determine the risk of stroke and the treatment [30].

The predictive scores do not incorporate imaging findings which have been shown to have predictive value. CT results can improve prediction [31]. In spite of the transient nature of the symptoms, diffusion-weighted imaging (DWI) has identified areas of acute brain ischaemia in about half the patients and with symptoms such motor impairment. The presence of multiple DWI lesions of varying ages suggests active early recurrence over time and portends a higher early risk of future ischaemic events [32]. In addition to ABCD2 score, taking DWI into account improves the prediction of early risk of stroke after TIA [33]. The results suggest DWI evaluation should be done urgently after TIA [34], and the National Stroke Association guidelines suggest to include imaging at some point [35].

Current international guidelines have adopted the ABCD2 score in risk stratification of patients with TIA [36]. Two large population studies investigating the diagnostic utility of ABCD2 for prediction of early risk after TIA and to evaluate whether carotid stenosis or atrial fibrillation might add to the prognostic yield of ABCD2 score noted that the degree of carotid stenosis was linearly associated with increased stroke risk after TIA, whereas atrial fibrillation was not [37, 38]. This highlights the importance of carotid evaluation in all TIA patients independent of the presenting ABCD2 scores [36].

Management

For a new-onset TIA patient, an ABCD2 can be a guide in the management, and patients with a score of 4 or more crescendo TIA, atrial fibrillation and those on anticoagulants should be referred to the hospital for prompt evaluation and treatment [39]. The EXPRESS Study [40] demonstrated that intense and immediate medical treatment of TIA reduced the early risk of stroke by 80%. There is still however no consensus on the urgent treatment of TIA. A new-onset TIA patient with an ABCD2 score of 3 or higher should according to the American Heart Association Guidelines be referred to the hospital immediately for emergent diagnostic evaluation. Low-risk patients with ABCD2 score below 3 can be managed by a

specialist or referred to a neurological/TIA clinic and be seen within 7–10 days.

The mainstay of management of TIA following acute recovery is diagnosis and treatment of the underlying cause. The family physicians are advised to give aspirin at the time of diagnosis. CT scan must be done to exclude haemorrhage before commencement of antithrombotic therapy. Specialist assessment confers the diagnosis usually with cerebral imaging [41]. The American Heart Association (AHA) and the American Stroke Association (ASA) and the more recent guidelines from the 8th American College of Chest Physicians Conference on Antithrombotic and Antiplatelet therapy recommend aspirin, clopidogrel or extended-release dipyridamole (ER-DP) plus aspirin as accepted first-line options for secondary prevention of ischaemic events in patients with a history of TIA or stroke [42]. For patients with noncardioembolic TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce cardiovascular events or recurrent stroke. The recommended dose is aspirin (50–325 mg/day) monotherapy or combination of aspirin and extended-release dipyridamole and clopidogrel monotherapy according to the AHA/ASA recommendations [43].

The ESPS-2 trial demonstrated that aspirin 25 mg twice daily and dipyridamole in a modified release form at a dose of 200 mg twice daily have each been equally effective for the secondary prevention of stroke and TIA [44]. When coprescribed the protective effects are additive. The combination being more significantly effective than either agent prescribed singly [44, 45]. Low-dose aspirin does not eliminate the propensity for induced bleeding [44] and in patients who are aspirin intolerant, clopidogrel is another option but is said to have less advantage over aspirin than aspirin plus ER-DP, and its combination with aspirin has only marginally better efficacy and increased bleeding risks [46].

Impact

In one-third of the patients with TIA, no further symptoms are experienced, one-third continue to have TIAs, and the remaining one-third have completed strokes [15]. Those with TIA and hypertension experienced higher stroke incidence rates, and 13% of those with TIA had evidence of cardiovascular disease [8]. TIA poses considerable difficulty in diagnosis and diagnostic uncertainty is common. People's quality of life and their perception of health may change permanently following a TIA [47]. Those who have had a TIA or minor stroke may experience distress and residual functional impairment [48]. TIA can have a long-term impact, and it had been reported that TIA patients visited their general practitioners more frequently for fatigue, cognitive impairment and anxiety or depression [49]. It has been reported that life expectancy was lower than that of the general population following a TIA [50] (Box 1).

Box 1 Key Points. Transient Ischaemic Attack

The definition of TIA has unfolded to focal dysfunction with no imaging evidence of acute infarction, according to the AHA/ASA 2009 Guidelines [2].

In one-third of the patients with TIA, no further symptoms are experienced, one-third continue to have TIAs, and the remaining one-third have completed strokes [15].

In another study, 10–20% of the patients with TIA had a stroke within 90 days and in about half of them the stroke occurred within 24–48 h [16].

There are many non-vascular conditions that may cause symptoms suggestive of TIA or stroke and have often been referred to as 'TIA mimics' or 'stroke mimics' [17].

Presently a validated score – the ABCD2 score – is from five factors with 7 points [28]. The risk of stroke within 2 days following TIA with a score between 0–3 is 1%, 4–5 is 4.1% and 6–7 is 8.1%, respectively [28].

The EXPRESS Study demonstrated that intense and immediate medical treatment of TIA reduced the early risk of stroke by 80% [40].

Carotid evaluation in all TIA patients is important and independent of the presenting ABCD2 scores [29].

(*continued*)

Box 1 Key Points. Transient Ischaemic Attack (continued)

A new-onset TIA patient with an ABCD2 score of 3 or higher should according to the American Heart Association Guidelines be referred to the hospital immediately for emergent diagnostic evaluation.

Aspirin 25 mg twice daily and dipyridamole in an extended release form at a dose of 200 mg twice daily have each been equally effective for the secondary prevention of stroke and TIA [44].

Multiple Choice Questions

1. The following in relation to transient ischaemic attack (TIA) are true, *except*:
   A. The stroke rate is more than 30% in the 90 days of TIA.
   B. Intense and immediate medical treatment of TIA reduces the risk of stroke by 80%.
   C. Carotid evaluation in all TIA patients is important and independent of the presenting ABCD2 scores.
   D. For non-cardioembolic TIA, antiplatelet agents are recommended.

MCQ Answers

1 = A

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Primary and Secondary Prevention of Stroke

79

Contents

Abstract

The risk of first stroke and recurrence of stroke can be reduced by interventions that modify the treatable cardiovascular and cerebrovascular risk factors. The most important risk factor for stroke is age, and in both men and women, the stroke rate doubles for each successive 10 years after the age of 55. The risk factors for stroke may be different for the two sexes, ethnic groups and stroke subtypes. A proper understanding of the risk factors is essential for the primary prevention of stroke. Hypertension, congestive heart failure, coronary artery disease and atrial fibrillation are the four major risk factors apart from age. Atrial fibrillation (AF) becomes more prevalent with age in the general population, and the extent of stroke associated with AF increases with age. The present review will highlight the improvements that have occurred in the prevention of stroke.

Keywords

Stroke · Recurrence of stroke · Risk factors for stroke · Atrial fibrillation · Anticoagulation

Introduction

The risk of first stroke and recurrence of stroke can be reduced by interventions that modify the treatable cardiovascular and cerebrovascular risk

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_78

factors. Each year, it is estimated that there are about 40,000–48,000 stroke events among Australians, and about 12,000 suffer a recurrence each year [1]. Primary and secondary preventive measures are important for the elderly because of the various impacts on the morbidity, mortality and quality of life. The most important risk factor for stroke is age, and in both men and women, the stroke rate doubles for each successive 10 years after the age of 55 [2]. The more important risk factors are hypertension, myocardial infarction, atrial fibrillation, diabetes mellitus, dyslipidaemia and asymptomatic carotid artery stenosis. These risk factors for stroke may be different for the two sexes, ethnic groups and stroke subtypes [3]. Some of the risk factors such as age, gender, race and hereditary factors are non-modifiable. The four lifestyle factors identified are cigarette smoking, alcohol consumption, diet and physical inactivity.

Primary Prevention of Stroke

A proper understanding of the risk factors is essential for the primary prevention of stroke. Hypertension, congestive heart failure, coronary artery disease (CAD) and atrial fibrillation are the four major risk factors apart from age.

Hypertension

The elderly are at high risk for morbidity and mortality from hypertension-related diseases, and several studies have shown that treatment of hypertension (isolated systolic hypertension, systolic/diastolic) in patients >60 years of age is extremely effective in primary prevention especially through the treatment of systolic hypertension [4]. Hypertension manifesting as systolic hypertension should be treated aggressively [5]. Hypertension is strongly related to stroke, coronary artery disease (CAD) and renal disease. For every 7.5 mm Hg increase in diastolic blood pressure, CAD risk increases by 29% and stroke risk by 46% [6]. It is a modifiable risk factor, and its treatment reduces the risk of stroke. Randomized controlled trials of treatment of hypertensive patients 80 years and older had revealed by lowering the blood pressure, the total mortality could be reduced by one-fifth and the rates of cardiovascular events by one-third [7]. There was a reduction in the incidence of stroke (25%) and CAD events (19%) in subjects aged 65–74 with hypertension treated as compared with the placebo group [8]. The initiation of hypertensive therapy for the 80 years and older are not well defined and should follow the guidelines from The Seventh Report of the Joint National Committee [9].

Heart Failure (HF) and Coronary Artery Disease (CAD)

After the age of 65, the incidence of heart failure approximates 10 per 1000 people rising to 100 per 1000 people in those over 80 years [10]. People with heart failure are twice as likely to die from a stroke than the general population. In the community, people with heart failure have an increased risk of ischaemic stroke compared with the general population. Stroke results in more than a twofold increase in mortality [11]. Coronary heart disease, heart failure, dilated cardiomyopathy and heart valve disease have increased risk of stroke.

Atrial Fibrillation

Atrial fibrillation (AF) becomes more prevalent with age in the general population, and the extent of stroke associated with AF increases with age [12]. There is a 17-fold increased risk of stroke with rheumatic mitral valve disease with AF. Depending on the type of valve, patients with prosthetic valves will require anticoagulation usually with a higher INR. Non-valvular atrial fibrillation (NVAF) increases the risk of stroke by about six times [13, 14]. Patients with AF are at increased risk of stroke, and in patients with NVAF, the risk of ischaemic stroke averages 5% per year, about three to five times that of people in sinus rhythm [13]. The risk of stroke in patients

with AF increases with age [15]. Those above 75 years or over or with specific risk factors are at highest risk for stroke [16]. AF affects about 10% of the elderly over the age of 80 years [17]. The annual risk for stroke increases with increasing age from 11.5% in ages 51–59 to 23% in ages 80–89 [13].

Oral anticoagulation is required in patients with NVAF who have specific risk factors for stroke such as age, previous TIA/stroke, hypertension, diabetes mellitus, heart failure and coronary artery disease. More recently, the Atherosclerosis Risk in Communities (ARIIC) study indicated that premature ventricular complexes (PVCs) were associated with new onset of atrial fibrillation and death [18], and an association between PVCs and stroke have been reported earlier. PVCs detected on a rhythm strip may be a newly identified marker [19], if not a risk factor for stroke.

CHADS score or CHADS2 score is one method of determining the risk of stroke in patients with AF in primary prevention and as a basis to determine the degree of anticoagulation therapy. The score distinguishes between patients with high risk and low risk of stroke [20, 21]. Many clinicians feel that age over 75 years is equally a potent risk factor as a history of previous stroke. The European Society of Cardiology (ESC) has recognized this inequality of risk in the CHADS and had put out a more detailed risk assessment tool, the CHA2DS2-VASc score [22], and the CHADS2 score has now been superseded by the former. The CHA2DS2-VASc score has significantly improved the classification of AF patients at low and intermediate risk of stroke [23]. A score of 2 or more is of moderate or high risk and anticoagulation is recommended.

Patients with AF who are on medical prophylaxis are at high risk of bleeding complications, and it is important to evaluate the risk of bleeding. The European Society of Cardiology in its guidelines released the HAS-BLED score to assess the bleeding risk [24]. A score of more than 3 indicates high risk [25]. In the elderly, it has been suggested that HAS-BLED has better predictive value [26].

Warfarin is recommended in high-risk patients to prevent thromboembolism unless the drug is contraindicated. Warfarin is the more effective although aspirin is most commonly used as an alternative to warfarin. In selected patients, an anticoagulant with a direct thrombin inhibition, dabigatran may be an alternative to vitamin K antagonists like warfarin. Other effective substitutes for warfarin include factor Xa inhibitors such as apixaban betrixaban and rivaroxaban. Dabigatran has been shown to be equally effective as warfarin in stroke prevention in atrial fibrillation [27]. The randomised evaluation of long-term anticoagulation study (RELY study) studied patients with non-valvular AF and at least one risk factor of stroke. The lower dose of 110 mg twice daily showed similar efficacy with warfarin in reducing stroke and reduced rates of major bleeding. Both doses however showed a significant reduction of intracranial haemorrhage of about 70% compared with warfarin [27]. Rivaroxaban has also been shown to be effective [28]. The main advantage of dabigatran and rivaroxaban compared to warfarin is that no routine anticoagulation monitoring is required. Furthermore, single-dose regimen irrespective of age, gender and body weight should befit most patients. However in case of bleeding, there is no antidote available for dabigatran and rivaroxaban.

More recently life-threatening haemorrhage has been reported in the elderly with poor renal function taking dabigatran [29, 30]. In the old age group due to age-related decline in the creatinine clearance, there is accumulation of dabigatran, and hence safe dosing in the elderly will depend on the creatinine clearance. The Cockcroft-Gault formula is the most appropriate method to calculate the creatinine clearance [31]. Older patients with AF should be treated cautiously irrespective of the medication chosen because of the increased risk of stroke and bleeding and possible drug interactions [17]. Warfarin however remains the drug of choice in patients with rheumatic mitral valve disease, left ventricular thrombi, mechanical valves and severe renal dysfunction [17].

Diabetes Mellitus

It is estimated that the risk of stroke increases by 1.5- to 3-fold for patients with diabetes [32–34],

and diabetes also doubles the risk of stroke recurrence [35] with poor stroke outcome. Diabetes and stroke together are a major cause of mortality and morbidity worldwide. Many diabetics have hypertension, high cholesterol and increased body weight which increase the stroke risk even more. Diabetic subjects have a very high risk of death from stroke particularly women [36]. In the Collaborative Atorvastatin Diabetes Study (CARDS), a randomized trial on type 2 diabetic patients without high LDL cholesterol but with one other risk factor received placebo or atorvastatin 10 mg daily. Those on atorvastatin treatment showed a significant reduction in the incidence of new stroke by 48% independent of patient's age, gender, cholesterol and blood pressure [37].

Asymptomatic Carotid Artery Stenosis

The Asymptomatic Carotid Atherosclerosis Surgery (ACAS) trial showed an absolute risk reduction for stroke and death of 5.9% over 5 years with carotid endarterectomy (CE) compared with medical treatment alone in patients with 60–99% asymptomatic stenosis [38]. The Asymptomatic Carotid Artery Stenosis Trial (ACST) also came up with the almost identical result with 5.4% absolute stroke risk reduction [39]. Several guidelines do not support CE for asymptomatic carotid artery disease. The ACAS and ACST show that elective CE performed by a skilled surgeon is an option when medical management had failed. The American Heart Association guideline however recommends CE for asymptomatic lesions of at least 60% stenosis [40]. Data from randomized controlled studies regarding the efficacy of CE in older patients are limited. NASCET for instance was limited to patients aged <80 years, and only 14% were >75 years. Similarly only 6% of all were >75 years in the ACST. It has been shown recently that there is increasing evidence that the risk of stroke has fallen with best medical treatment alone in patients with severe asymptomatic carotid artery stenosis [41, 42]. It is believed that surgery has little to offer except in those patients with a high risk of stroke on medical treatment alone [43].

Dyslipidaemia

Epidemiological studies have indicated a link between total cholesterol levels and ischaemic stroke [44, 45]. Unlike the association between lipoprotein levels and coronary artery disease, no strong correlation between plasma lipoprotein concentrations and risk of stroke has been clearly established [46]. More recently it has been seen that there is an increased risk of new-onset diabetes by 12% with intensive-dose statin therapy compared with moderate-dose statin therapy [47]. In high-risk elderly subjects < or = 82 years of age, the largest trials suggest a favourable effect with the use of statins [4]. Nevertheless, the treatment of dyslipidaemia for the primary dysfunction of ischaemic stroke is based on the recommendations of the National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATPIII) [48].

Lifestyle Factors

i. Cigarette smoking

Cigarette smoking has been shown to be an independent determinant of ischaemic stroke [49, 50]. It is also an independent determinant of carotid artery plaque thickness [51]. The risk of stroke increases with the number of cigarettes smoked. Smoking cessation medications and counselling should be offered to all those who smoke.

ii. Alcohol consumption

A J-shaped relationship has been shown between alcohol use – a protective effect in light or moderate drinkers – and an elevated stroke risk with heavy alcohol consumption [52]. Alcohol may increase the risk of stroke through various mechanisms that include hypertension, cardiac arrhythmias, reduction in cerebral blood flow and hypercoagulable states.

iii. Physical activity

Regular exercise improves functional capacity and reduces the risk of premature stroke from cardiovascular disease. It has been reported as a protective effect on stroke

in both men and women [53, 54] and that moderate physical activity is more protective against ischaemic stroke than light activity [55]. The ability of exercise training to reduce the mortality and morbidity rates has not been well established for elderly patients. The role of physical activity as a risk factor for stroke is likely mediated through its role in controlling other risk factors such as hypertension, diabetes mellitus and obesity.

iv. Diet

High sodium intake was significant and an independent factor for both cerebral haemorrhage (ICH) and cerebral infarction (CI) in one study [56]. An Australian study reported that additional salt intake increased the risk of ICH but not CI [57].

Secondary Prevention of Stroke

Secondary prevention of stroke includes treatment of hypertension, hyperlipidaemia, antithrombotic therapy for atrial fibrillation and carotid endarterectomy in patients with severe carotid artery stenosis Effective secondary prevention depends on a number of factors such as stroke subtypes, aetiological mechanisms and appraisal of the cardiovascular risk profile are imperative [3]. For providing of optimal secondary prevention interventions, age should not be considered a barrier [58].

Hypertension

The perindopril protection against recurrent stroke study (PROGRESS) demonstrated that patients who have had a stroke or TIA on an average 6 months previously and with hypertension when treated with perindopril 4 mg in combination with indapamide 2 mg or 2.5 mg at the end of 4 years, the relative risk of stroke was reduced by 28% with similar reduction in all cardiovascular morbidity. The lowest tertile of mean blood pressure was 128/77 mmHg at the point of entry. Patients with intracerebral haemorrhage benefited more than those with ischaemic events [59]. What the trial further showed was that irrespective of the starting blood pressure levels all patients may benefit from treatment to reduce the pressure. The perindopril and indapamide appeared to have been well tolerated as 90% of patients continued to take the treatment for 4 years [9].

Another factor is that in patients with moderate to severe carotid artery stenosis, perindopril may reduce the blood pressure without reducing the global cerebral blood flow. It is now appreciated that TIA and minor stroke have a higher risk of subsequent stroke than before; the 7-day risk is between 8% and 12% and could be as high as 20% in some groups [60, 61]. Whether the benefits of secondary prevention pharmacotherapy extend to the very early period is unclear [62]. Lowering the blood pressure following an acute stroke should be delayed by at least 5–6 days after the onset of the stroke. In the elderly, the blood pressure can be lowered with the same agents used among the younger age with preference for thiazide diuretic/angiotensin-converting enzyme inhibitor combination has proven beneficial [58], and antihypertensive therapy may be as effective as antithrombotic drugs in the secondary prevention of stroke [3].

Atrial Fibrillation (AF)

The recurrence rate is approximately 12% per year for subsequent 2–3 years for patients with atrial fibrillation and with a history of recent or remote ischaemic stroke. The more important cardiovascular causes are valvular heart disease, ischaemic heart disease, cardiomyopathies, atrial septal defect, pericarditis and infiltrative heart diseases such as amyloidosis and endomyocardial fibrosis. The non-cardiovascular causes are hyperthyroidism, pulmonary embolism, idiopathic ‘lone’ AF, drugs, alcohol, caffeine and pheochromocytoma.

Diabetes

Diabetes is a clear risk factor for stroke [63]. Diabetes and age were independent predictors of

recurrent stroke in a population-based study of stroke from Rochester, Minn [64]. Diabetes doubles the risk of stroke recurrence [59] with poor outcome. Diabetes and stroke together are the major causes of morbidity and mortality worldwide.

Transient Ischaemic Attack

The American Heart Association and American Stroke Association (AHA/ASA) in 2008 updated the earlier recommendations for the prevention of stroke in patients with stroke and transient ischaemic attack [65] based on recent trials. They especially looked at two areas requiring modifications, namely, (i) the use of specific antiplatelet agents for stroke prevention in patients with history of noncardioembolic ischaemic stroke or TIA and (ii) the use of statins in their prevention of recurrent stroke. Antiplatelet agents rather than oral anticoagulants were recommended for patients with noncardioembolic stroke or TIA. Aspirin (50–325 mg/day) was the new recommendation as monotherapy, and the combination of aspirin and extended release of dipyridamole and clopidogrel monotherapy as appropriate for initial therapy. Based on the stroke prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial for patients with atherosclerotic ischaemic stroke and TIA and without known coronary heart disease, intensive lipid therapy was recommended to reduce risk of stroke and cardiovascular events [66] (Box 1).

Box 1 Key Points: Prevention of Stroke

Apart from age, hypertension, coronary artery disease, atrial fibrillation, diabetes, dyslipidemia, and asymptomatic carotid artery stenosis are high risk factors for stroke in the elderly.

The life style factors include smoking, alcohol consumption, physical inactivity, and diet.

The CHADS2 score is used to determine the risk of stroke patients with AF in primary prevention as well as a basis to determine the degree of anticoagulant therapy. The CHA2DS2-VASc is a more embracing risk assessment tool [23].

Warfarin is recommended in high risk patients with AF unless the drug is contraindicated.

Dabigatran is easier to use and equally effective and no routine monitoring is required.

It is meaningful to evaluate the risk of bleeding when anticoagulation is contemplated and the HAS-BLED score is useful to assess the risk of bleeding [24].

Box 1 Key Points: Prevention of Stroke (continued)
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It is meaningful to evaluate the risk of bleeding when anticoagulation is contemplated, and the HAS-BLED score is useful to assess the risk of bleeding [24].

Multiple Choice Questions

1. The following are true in relation to prevention of stroke, *except*:
   A. Non-valvular atrial fibrillation (NVAF) increases the risk of stroke by about six times.
   B. Oral anticoagulation is required for patients with NVAF who have specific risk factors such as age, TIA/stroke, hypertension, diabetes, heart failure and coronary artery disease.

C. Antiplatelet agents rather than oral anticoagulants are recommended for patients with noncardioembolic stroke or TIA

*D. The efficiency of statin in primary prevention has not been demonstrated.

2. The following are true with regard to prevention of stroke, *except*:
   A. Patients 80 years or more should not be excluded from carotid endarterectomy solely on age.
   B. In the elderly, patient with AF with risk factors for stroke and rate control with anticoagulation is as good as rhythm control.
   C. In patients with permanent (chronic) AF, electrical cardioversion is not an option to restore sinus rhythm in the elderly.
   D. The novel anticoagulants are equally effective and have equal safety profile as warfarin.

MCQ Answers

1 = D; 2 = C

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Carotid Artery Disease in the Elderly 80

Contents

Abstract

Extracranial carotid artery disease is the cause of stroke in 14–40% of patients, and artery to artery embolism is the main mechanism of ischaemic stroke. The association of carotid artery disease with coronary artery disease, peripheral vascular disease, atheromatous renal artery stenosis, aortic-iliac occlusive disease and history of cerebrovascular disease is well documented. The finding of an audible carotid bruit in an asymptomatic patient may be the first indication for further evaluation, but they are not a reliable indicator of asymptomatic stenosis. A variety of imaging procedures are available, relatively safe and reliable, and each technique however has its usefulness and its shortcomings. Medical treatment alone is now considered the best treatment for asymptomatic carotid artery stenosis except in those patients who are at risk of stroke.

Keywords

Extracranial carotid artery disease · Audible carotid bruit · Asymptomatic carotid artery stenosis · Carotid endarterectomy (CEA) · Percutaneous transluminal carotid angioplasty · Carotid stents

Introduction

Extracranial carotid artery disease is the cause of stroke in 14–40% of patients, and artery to artery embolism is the main mechanism of ischaemic stroke [1]. The association of carotid artery disease with coronary artery disease [2], peripheral vascular disease [3], atheromatous renal artery stenosis [4], aortic-iliac occlusive disease [5] and history of cerebrovascular disease is well documented. There is a high prevalence of significant internal carotid stenosis ranging from 1.3 to 8.5% in

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_80

patients undergoing cardiac surgery [6, 7]. Patients undergoing aortic reconstruction are commonly found to have internal carotid artery (ICA) disease. Age, male gender [8, 9, 10], total cholesterol [5, 10] and smoking [10] are all independent predictors of carotid artery disease. There are differences in the prevalence of symptomatic carotid stenosis between ethnicities. There are reports of higher prevalence of carotid stenosis in Blacks compared to White stroke patients [11].

The carotid artery can be involved by a number of different pathologies, atherosclerotic carotid artery disease, carotid artery stenosis, spontaneous carotid artery dissection, carotid artery tortuosity and kinking and atherosclerotic aortic arch disease, traumatic occlusion and inflammatory arteriopathies [12]. The ICA and ECA branches of the common carotid artery are the common sites for plaque formation in the cerebrovascular system. Atherosclerosis is one of the main risk factors for ischaemic stroke. Carotid artery disease results from atherosclerosis leading to plaque formation, plaque ulceration, narrowing of vessels in thromboembolism and carotid embolic disease. Shear stress and turbulent flow have been shown experimentally to increase endothelial permeability [13]. Atherosclerotic disease of the aortic arch should be considered as a risk factor for ischaemic stroke and a possible source of cerebral emboli [14]. Aortic plaque is a manifestation of generalized atherosclerosis. In recent years, there is increasing evidence that besides embolism a compromised cerebral blood flow may contribute in causing TIA and stroke in patients with carotid artery occlusion. It can be surmised in this situation there could be failure of the collateral blood flow via the circle of Willis, the pial-pial collaterals and the ophthalmic artery.

Evaluation

The finding of an audible carotid bruit in an asymptomatic patient may be the first indication for further evaluation, but they are not a reliable indicator of asymptomatic stenosis [15]. Only about one-third of the patients with a carotid bruit have haemodynamically significant stenosis (70–90%) [16]. The annual risk of ipsilateral infarction in patients with asymptomatic stenosis detected by US or angiography is approximately 1–2%, but stroke risk is higher when there is progressive stenosis and stenosis exceeding 75–80% [15]. The determination of vessels which may be diseased is crucial for patient management especially if carotid endarterectomy is contemplated. A variety of imaging procedures are available, relatively safe and reliable, and each technique however has its usefulness and its shortcomings.

Carotid-Doppler ultrasonography (C-DUS) is used to detect luminal narrowing based on the velocity of blood flow across a stenotic lesion and other structural details of the carotids [17]. Although it has high sensitivity and specificity for detecting significant stenosis of the internal carotid (ICA) [18], it is less so in determining stenosis less than 50%. Furthermore the intracranial part of the ICA cannot be evaluated. *Transcranial Doppler (TCD)* detects and quantifies intracranial vessel stenosis, occlusions, collateral flow, embolic events and cerebral vasospasm [19, 20]. TCD is capable of detecting microembolic signals originating from conditions which are associated with microemboli such as carotid stenosis, atrial fibrillation, patent foramen ovale, prosthetic heart valves and plaque in the aortic arch [17]. It is painless, non-invasive, safe [17] and cheap and can be performed by portable machines.

Computed tomographic angiography (CTA) is found to have a high sensitivity and high negative predictive value for carotid disease. It appears to be an excellent screening test for ICA stenosis and was advocated to be included in the initial imaging of patients with acute ischaemic stroke [21]. Its accuracy for detecting intraarterial thrombus is close to that of DSA [22] which remains the gold standard for detection of many types of cerebrovascular lesions and diseases. Another study however found the tendency of CTA to overestimate the degree of stenosis [23].

Contrast material enhancer-*magnetic resonance angiography (CE-MRA)* has good sensitivity for detecting high-grade stenosis. It produces an image of the artery. It is expensive, time-consuming and not readily available. In cerebral angiography, DSA is the gold standard for imaging the carotid arteries, and it allows evaluation of

the entire carotid artery system. It provides information about plaque morphology and collateral circulation. It is invasive, is expensive and can cause serious complications such as stroke and death [17]. The degree of stenosis is determined with high degree of accuracy by CTA and DSA with the latter superior to CTA [17].

Management

Carotid Endarterectomy (CEA)

Based on studies the American Heart Association [24] recommends: A symptomatic ipsilateral carotid stenosis of 70–99% is a proven indication for carotid endarterectomy (CEA) provided the surgical risk does not exceed 6%. For symptomatic patients with 30–60% stenosis, CEA is acceptable but has not been proven to be of benefit. For symptomatic patients with 0–29% stenosis, CEA is not beneficial. Asymptomatic patients with stenosis 60–99% are considered to have a proven indication for CEA provided the surgical risk is less than 3% and life expectancy is not less than 5 years. Increase risk of CEA has been reported with advancing age [25, 26], but the fear that elderly patients have a higher risk of CEA-related stroke has not been supported from the review of contemporary literature, and it appears that mortality concern is related to associated comorbidities [27].

There is now increasing evidence that the risk of stroke in patients with asymptomatic carotid artery stenosis on medical treatment alone has fallen [28]. Medical treatment alone is now considered the best treatment for asymptomatic carotid artery stenosis [29] except in those patients who are at risk of stroke.

Percutaneous Transluminal Carotid Angioplasty and Carotid Stents

Age is a risk factor for CEA especially in those 80 years and over. Carotid artery stenting (CAS) frequently with filter devices has emerged as an alternative to carotid endarterectomy (CEA) for treating carotid stenosis. However, there is an increasing risk of perioperative stroke and death with CAS with increasing age and treatment within 2 weeks of neurological symptoms in symptomatic patients [30]. CAS is also associated with increased peri-procedural complications [31]. Despite the use of distal protection devices, CAS is associated with a higher burden of microemboli compared to CEA [32].

Patients with complete occlusion of the carotid artery, previous stroke with dense neurological deficit, severe comorbidity and a haemorrhagic component to their stroke are excluded from CEA. There is a variable risk of stroke or death in the perioperative period. Cardiac events are the most common cause of mortality, and hence pertinent preoperative workup is crucial. In a trial in which surgeons were carefully selected, the permanent disabling stroke and death rate was 2.3%, and the rate of perioperative stroke and death was 5.3% [33]. In patients undergoing CEA, the following are recognized as predictors of adverse events: age above 75 years, symptom status, severe hypertension, angina, evidence of ICA thrombus or stenosis near the carotid siphon and endarterectomy performed in preparation for coronary bypass surgery [34]. Perioperative stroke was clearly technically related in 65% of the cases and unrelated to patient's age, sex or associated problems [35]. Technical failure would be enhanced by the presence of hypertension, preoperative neurological deficits and contralateral carotid occlusion resulting in perioperative stroke [36].

Thrombolysis or mechanical recanalisation has been used to restore blood flow following acute ischaemic stroke. In some patients, reperfusion gives rise to cerebral reperfusion injury resulting in oedema and haemorrhage, and this can occur as a complication of carotid endarterectomy or intracranial stenting. Several mechanisms have been proposed in the pathogenesis of reperfusion injury such as dysautoregulation.

Impact

Extracranial carotid artery disease is the cause of stroke in 14–40% of patients, and artery to artery embolism is the main mechanism of ischaemic

stroke. A study comparing learning and memory skills in patients with 50% reduction in the diameter of the carotid artery with subjects with normal blood flow showed that those with carotid artery disease overall performed poorly in thinking skills and memory [37]. The morbidity and mortality increase in patients with carotid artery occlusion undergoing coronary bypass operations [38, 39] (Box 1).

Box 1 Key Points. Carotid Artery Disease in the Elderly

Extracranial carotid artery disease is the cause of stroke in 14–40% of patients, and artery to artery embolism is the main mechanism of ischaemic stroke [1].

In recent years, there is increasing evidence that besides embolism a compromised cerebral blood flow may contribute in causing TIA and stroke in patients with carotid artery occlusion.

Based on studies, the American Heart Association [24] recommends: A symptomatic ipsilateral carotid stenosis of 70–99% is a proven indication for carotid endarterectomy (CEA) provided the surgical risk does not exceed 6%.

For symptomatic patients with 30–60% stenosis, CEA is acceptable but has not been proven to be of benefit. For symptomatic patients with 0–29% stenosis, CEA is not beneficial.

Asymptomatic patients with stenosis 60–99% are considered to have a proven indication for CEA provided the surgical risk is less than 3% and life expectancy is not less than 5 years.

The fear that elderly patients have a higher risk of CEA-related stroke has not been supported from the review of contemporary literature, and it appears that mortality concern is related to associated comorbidities [27].

Medical treatment alone is now considered the best treatment for asymptomatic carotid artery stenosis [28, 29] except in those patients who are at risk of stroke.

Multiple Choice Questions

1. The following are true in relation to carotid artery disease, *except*:
   A. The degree of stenosis can be determined with a high degree of accuracy by CTA or DSA with the latter superior to CTA.
   B. A symptomatic ipsilateral carotid stenosis of 70–90% is a proven indication for carotid endarterectomy.
   C. Medical treatment alone is now considered the best treatment for asymptomatic carotid artery stenosis except in those who are at risk of stroke.
   D. Cognitive function improves after carotid arterectomy.
2. The following are true in relation to carotid artery disease, *except*:
   A. Patients over the age of 80 years should be considered 'high risk' for carotid endarterectomy.
   B. Embolic events during carotid artery stenting might be less than observed during carotid endarterectomy.
   C. Reperfusion injury after carotid endarterectomy and carotid artery stenting is due to mechanisms such as dysautoregulation.
   D. Atherosclerotic disease of the aortic arch should be considered as a risk factor for ischaemic stroke and possible source of emboli.

MCQ Answers

1 = D; 2 = B

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Part XVIII

Hearing Loss and Related Problems in the Elderly

Part XVIII provides an overview of some of the problems relating to the ear that are common to this population, namely hearing impairment/loss, imbalance and vertigo and tinnitus. The review provides information on their prevalence and mechanisms, evaluation, and clinical care. In the elderly, chronic hearing loss is the third prevalent condition. Hearing impairment adversely affects the quality of life of the elderly. Approximately 50% of Australians over the age of 65 years have hearing impairment. Presbycusis is the most common type of hearing impairment in the elderly and is age-related affecting about 40% of individuals 75 years or older. The overall incidence of dizziness, vertigo, and imbalance increases with age and is a common symptom in at least one-third of the patients over the age of 65 years. Prevalence estimates of persons with tinnitus vary widely from 7.9 million to more than 37 million.

Common Ear Problems in the Elderly

81

Hearing Loss in the Elderly

Contents

Abstract

This chapter provides an overview of some of the problems relating to the ear that are common to this population, namely, hearing impairment/loss, imbalance and vertigo and tinnitus. In the elderly, chronic hearing loss is the third prevalent condition. Presbycusis is the most common type of hearing impairment in the elderly and is age related affecting about 40% of individuals 75 years or older. The quality of life and functional ability are largely dependent on the preservation of hearing in elderly persons.

Keywords

Hearing impairment/loss · Imbalance · Vertigo · Tinnitus · Sensorineural hearing loss · Presbycusis

Introduction

It is often difficult to distinguish changes of normal ageing from those of other contributing factors [1]. Hearing depends on the integration of three processes – the peripheral comprising the external ear, middle ear and inner ear, auditory nerve and the central auditory processing (the brainstem and cortex). With ageing, there are a number of structural and pathophysiological processes associated with changes to functional components of the ear. Some of the common problems relating to the ear in the elderly are (1) hearing impairment/loss, (2) imbalance and vertigo and (3) tinnitus.

In the elderly, chronic hearing loss is the third prevalent condition [2]. Approximately 50% of

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_83

Australians over the age of 65 years have hearing impairment [3]. It had been estimated that 24.2 million Americans had an auditory disorder in the year 2000 [4]. Some of the common causes of conductive deafness include cerumen, tympanosclerosis, otosclerosis and Paget's disease. Dysfunction in the sensory elements and neural structures in the inner ear, cochlear and auditory centres will give rise to sensorineural hearing loss and is the most common hearing impairment in adults [5]. Sensorineural hearing loss can be further subdivided into sensory (cochlear) or neural (retrocochlear) hearing loss. It is important to make the distinction because neural hearing loss is often caused by tumours which are potentially curable. Some of the more common causes of sensorineural hearing loss are shown in Boxes 1 and 2.

Box 1 Common Causes of Sensorineural Hearing Loss

Infection: viral infections, meningitis, syphilis

Neoplasms: acoustic neuroma, meningiomas, metastatic lesions

Ototoxicity: see Box 2.

Trauma: head injury, noise-induced cranial/ear surgery

Idiopathic: presbycusis, Meniere's disease, idiopathic

Box 2 Ototoxic medications

Antibiotics: aminoglycosides, erythromycin

Antimalarials: quinine

Antineoplastics: cisplatin, nitrogen mustard

Anti-inflammatory agents: aspirin, NSAIDs; Diuretics: loop diuretics

Presbycusis

Presbycusis is a slowly progressive bilateral and symmetrical sensorineural hearing loss that is most predominant at high frequencies. Presbycusis is the most common type of hearing impairment in the elderly and is age related affecting about 40% of individuals 75 years or older [6]. It may arise from loss of internal ear hair cells and to degeneration of the central auditory pathways. Besides the decline in the high frequencies (due to sensory cell loss), there is reduction in speech discrimination (due to loss of cochlear neurons) particularly in the presence of background noise resulting in significant communication difficulties [7].

Diagnosis

A detailed history is important and should include past or present ear infections, ear surgery, trauma and the use of ototoxic medications. This is followed by an otoscopic examination to remove occluding cerumen and for evidence of otitis media. The traditional 'whispered voice test' or 'watch tick test' in primary care have been shown to be inadequate [8]. The Hearing Handicap Inventory for the Elderly – Screening Version (HHIE-S) and the audioscope are effective screening instruments in the clinical setting [9]. The HHIE-S is a ten-item self-administered questionnaire [10]. Its sensitivity increases when combined with the pure-tone audioscope.

Noise-Induced Sensorineural Hearing Loss (NIHL)

Noise-induced hearing loss is hearing loss due to exposure to loud and repeated sounds over an extended period resulting in damage to the inner ear. The incidence and prevalence are not known specifically. According to the World Health Organization, it is the most common occupational illness, and its incidence is on the increase [11]. The prevalence is varied ranging from 7% in the Western nations to 21% in the developing countries [12]. NIHL generally affects both ears. Other causes of hearing loss like Meniere's disease and acoustic neuroma are described in ▶ Chap. 82, "Vertigo/Dizziness in the Elderly."

Evaluating Hearing Loss

The evaluation of hearing loss involves (1) medical history, (2) physical examination, (3) laboratory evaluation, (4) tests of clinical measurement of hearing and (5) other diagnostic tests as needed.

1. A clear patient history with respect to its mode of onset, whether gradual or sudden and unilateral or bilateral, and manner of progression, fluctuating or continuous. Associated symptoms such as dizziness, vertigo, unsteadiness, pain in the ear, ear discharge and tinnitus must be recorded. In the elderly, tinnitus is most commonly associated with hearing loss [13]. The medication list is vital. A history of ear infection, ear and intracranial surgery and injury to head or ear should be obtained. A history to exclude noise exposure at workplace, amplified music and impact noise such as explosion or gunshot. A family history of deafness or ear-related tumours must be known. General medical conditions such as diabetes, autoimmune or demyelinating disorders cardiovascular or cerebrovascular disease such as a stroke could cause impaired hearing.
2. Physical examination should include examination of the ear (the auricles, external auditory canals, tympanic membrane) as well as the head and neck. A thorough neurological examination is a requisite for hearing loss that may be the only presenting symptom of an acoustic tumour or could be a signal of other pathological processes such as Meniere's disease, demyelinating disease or an autoimmune disorder.
3. Routine laboratory tests would include a full blood count, sedimentation rate, thyroid function tests, blood sugar level for diabetes, fluorescent treponemal antibody test for syphilis and an autoimmune profile (RA factor, ANA) among others.
4. Clinical measurement of hearing can be carried out by the 'whispering test' and the 'watch tick test,' but they are thought to be inadequate. The Rinne and Weber tuning fork tests have practical application as hearing tests. Rinne's test complements Weber's test. They may be used to ascertain whether there is a conductive element to the hearing loss and may be used prior to obtaining audiometric data. A 512-Hz tuning fork is used. With Weber's test in conductive deafness, there is lateralisation to the affected side, and in sensorineural deafness, there is lateralisation to the unaffected side. Rinne's test measures air versus bone conduction. Normally air conduction is longer than bone conduction, and in conductive deafness, this is reduced. In sensorineural deafness, air conduction remains greater than bone conduction in both ears.

Diagnosis of presbycusis can be assisted by the Hearing Handicap Inventory for the Elderly – Screening Version (HHIE-S), which is a reliable robust method to identify hearing impairment in the elderly [9, 14] (Fig. 1). HHIE-S together with the audioscope has been found to be effective screening tools in the clinical setting [8]. The sensitivity and specificity determined in two locations, hearing centre and physician's office, revealed that with the audioscope the sensitivity was 94% and specificity 98% in hearing centre and was 72% for both at the physician's office [9]. The audioscope is a hand-held otoscope combined with an audiometer. Forty decibels (dB) are tested in both ears at the following frequencies: 500 Hz, 1,000 Hz, 2,000 Hz and 4,000 Hz, and the sensitivity of the audioscope has been found to be 94% [8]. Following the screening tests, audiograms are recommended. Pure-tone audiograms provide pure-tone test signals in the range from 125 to 8,000 Hz relayed through ear headphones. The thresholds for a series of frequencies are recorded. Normal decibel level is 0–20. A bone conduction vibrator could be placed behind the outer ear to determine any possible conductive loss. The audiogram helps to ascertain whether the hearing loss is unilateral or bilateral; the kind of hearing loss present, conductive, sensorineural or mixed; and at the what frequencies the loss occurs (Fig. 2). The audiometer may also contain an input for an external sound source, for example, for speech (speech audiometry), and includes speech discrimination and speech reception threshold.

	Yes (4)	Sometimes (2)	No (0)
1. Does a hearing problem cause you to feel embarrassed when meeting new people?			
2.Does a hearing problem cause you to feel frustrated when talking to members of your family?			
3.Do you have difficulty hearing when someone speaks in a whisper?			
4.Do you feel handicapped by a hearing problem?			
5.Does a hearing problem cause you difficulty when visiting friends ,relatives, or neighbours			
6.Does a hearing problem cause you to attend religious services less often than you would like?			
7.Does a hearing problem cause you to have arguments with family members?			
8.Does a hearing problem cause you difficulty when listening to TV or radio?			
9.Did you feel that any difficulty with your hearing limits or hampers your personal or social life?			
10.Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?			

Range of points, 0-40; 0-8-no self-perceived handicap; 10-22, mild to moderate handicap; 24-40-significant handicap
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Fig. 1 Hearing Handicap Inventory for the Elderly – Screening Version (HHIE-S)

Persons with sensorineural and speech discrimination hearing loss who do not meet the criteria of presbycusis, noise-induced or ototoxic medications could be evaluated by auditory brainstem response and acoustic immittance, the latter includes tympanometry and acoustic reflex testing. They help to differentiate whether the lesions are central, retrocochlear or cochlear. Tympanometry, although is not a hearing test, is used to assess the function of the middle ear. The auditory brain response is used to determine the intactness of the auditory pathway from the cochlea to the brainstem.

5. Imaging. The MRI is used to exclude retrocochlear pathology and provides good assessment of the internal auditory canal and bony changes in the canal walls [15]. MR imaging is less expensive and is the modality of choice in most patients with sensorineural hearing loss [16]. It is more practical and with the addition of fast spin-echo imaging (FSE) demonstrates changes in the internal auditory canal, cerebellopontine angle, cranial nerves and membranous labyrinth [16, 17]. High-resolution FSE is less expensive than gadolinium-enhanced T1 MRI and is equally sensitive [17]. Limited MRI of the internal auditory canals may be useful to screen for retrocochlear pathological conditions in patients with unilateral auditory symptoms and no dizziness [18]. Auditory brainstem response is used as a screening procedure but is not reliable in detecting small acoustic neuromas [15, 19] and is not appropriate as a primary test to screen for acoustic neuromas [20]. High-resolution computed tomography of the temporal bone is used in certain middle ear and

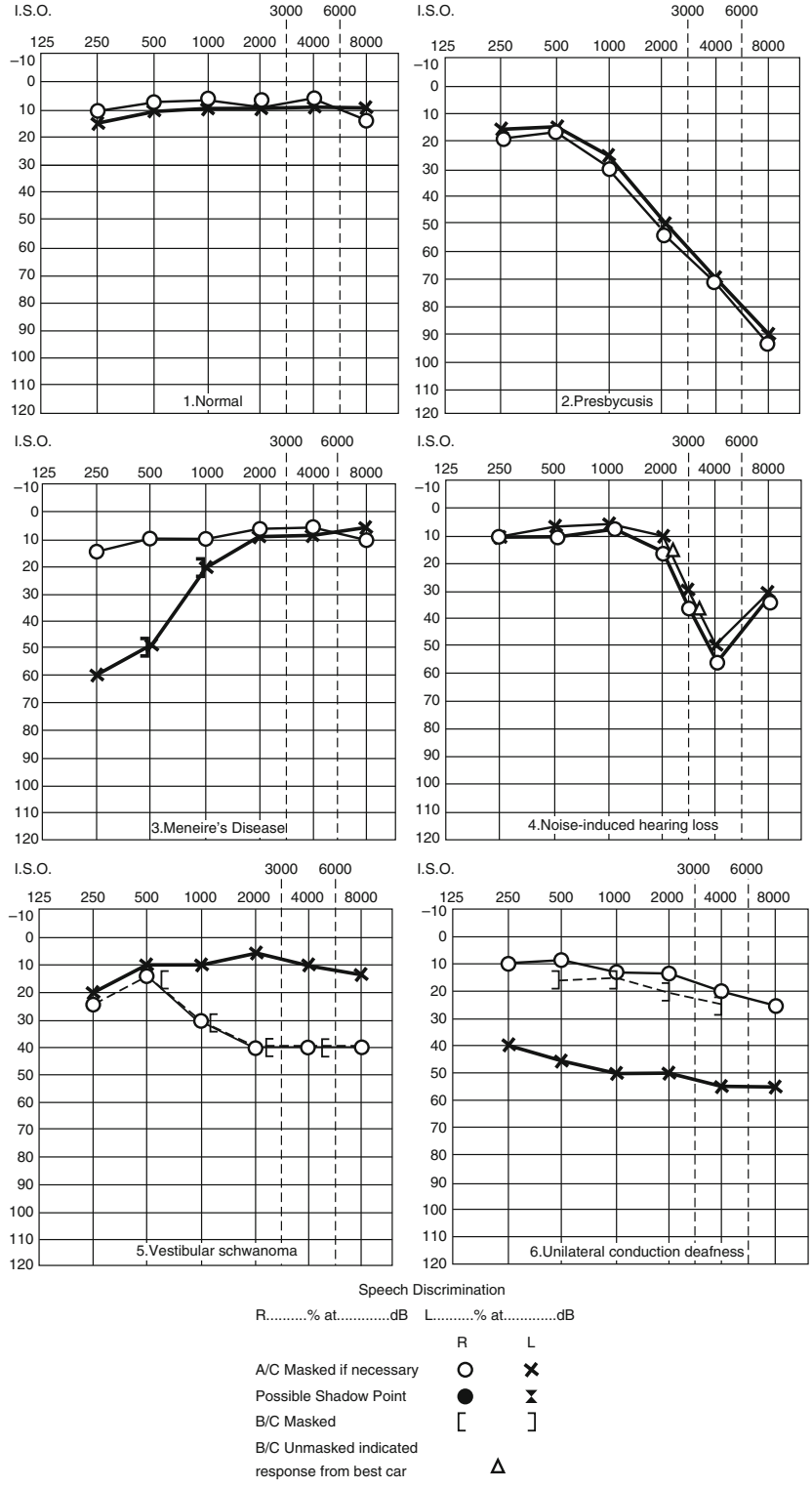

Fig. 2 (continued)

mastoid disorders, for example, glomus tumour and chronic infections.

Management

It is important to determine the hearing status prior to any diagnostic tool because of the existence of comorbidity of hearing loss and cognitive disorders [21]. Many adults ignore their hearing loss for years or decades because of the insidious nature of presbycusis [21]. The average age of first-time hearing aid wearer is around 70 years of age [22], and an average hearing age user waits over 10 years after the diagnosis to be fitted with the first hearing aid [23]. For effective communication, optimised hearing is crucial [22]. Early evaluation and treatment will allay the effects of hearing on quality of life and long-term health [21].

Impact

Hearing impairment adversely affects the quality of life of the elderly. It is the commonest cause of sensorineural deafness [24]. It had been reported that more than 30 million Americans are exposed to hazardous sound levels on a regular basis [25]. It is a costly occupational illness, and one-third of the total cost of hearing loss of about $ 11.6 billion is due to NIHL in Australia [26].The impact of hearing impairment can have serious consequences for social, functional and psychological well-being [6] and can create a psychological solitary confinement [27]. Hearing loss has been associated with whole range of reactions and can have a direct impact on mental health [27] such as embarrassment, fatigue, irritability, tension, stress, anger, depression, negativism and paranoia among others [22]. The quality of life and functional ability are largely dependent on the preservation of hearing in elderly persons. It causes serious communication difficulties limiting, for instance, occupational opportunities. This may have considerable physical, psychological and social consequences for the person, family and friends. Many older persons who are hard of hearing feel isolated or lonely within their own families [27]. Hearing impairment has been associated with decreased cognitive functioning in the elderly particularly Alzheimer's disease [8], and there is a strong correlation between the degree of hearing loss and risk of developing dementia [28]. There are a number of factors which may influence the ability of the individual to cope with hearing loss and will depend on factors such as mode of onset, severity, personality and communication demands [29]. Those with early-onset hearing loss report that they have incorporated the negative aspects of hearing loss into their personalities [27] (Box 3).

Box 3 Key Points: Hearing Loss

Presbycusis is the most common type of hearing impairment in the elderly and is age related affecting about 40% of individuals 75 years or older [6].

Sensorineural hearing loss that is most predominant at high frequencies.

According to the World Health Organization, NIHL is the most common occupational illness, and its incidence is on the increase [11].

A sudden hearing loss calls for an urgent referral to an otolaryngologist.

(*continued*)

Fig. 2 Audiometric configurations: (i) Normal – shows an almost straight line. (ii) Presbycusis – normal sensitivity at lower frequencies but poorer sensitivity for higher frequencies, 'sloping'. (iii) Meniere's disease – severe loss in the lower frequencies. (iv) Noise-induced hearing loss – loss in higher frequencies especially at 4 kHz. (v) Vestibular schwannoma – there is an asymmetric high-frequency sensorineural hearing loss. (vi) Unilateral conduction deafness – loss across a range of frequencies most commonly in one ear only

Box 3 Key Points: Hearing Loss (continued)

Sensorineural hearing loss which is asymmetrical and is gradually progressive on serial audiometry necessitates referral to an otolaryngologist.

Hearing Handicap Inventory for the Elderly – Screening Version (HHIE-S) is a reliable robust method to identify hearing impairment in the elderly [9, 14].

The MRI is used to exclude retrocochlear pathology [18].

Multiple Choice Questions

1. The following are true about hearing loss except:
   A. In presbycusis, the hearing loss is predominant at high frequencies.
   B. A sudden hearing loss requires urgent referral to otolaryngologist.
   C. In presbycusis, there is no reduction in speech discrimination.
   D. The total cost of noise-induced hearing loss is $11.6 billion in Australia.
2. The following are true of audiometric configurations except:
   A. In presbycusis, the configuration is a greatly sloping audiogram.
   B. In Meniere's disease, loss is in higher frequencies.
   C. In unilateral conduction deafness, there is loss across a range of frequencies.
   D. In vestibular schwannoma, there is an asymmetric high-frequency sensorineural hearing loss.
3. The following hearing tests are true except:
   A. 'Watch test' and the 'whisper test' are thought to be inadequate.
   B. In Weber's test in conduction deafness, there is lateralisation to the affected side and in sensorineural deafness to the unaffected side.
   C. In conductive deafness air conduction is longer than bone conduction.
   D. The audiogram helps to ascertain whether the hearing loss is unilateral or bilateral, kind of hearing loss and at what frequencies the loss occurs.

MCQ Answers

1 = C; 2 = B; 3 = C

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Vertigo/Dizziness in the Elderly

82

Contents

Abstract

It is a common symptom in at least one-third of the patients over the age of 65 years. Benign positional vertigo, vestibular neuronitis and Meniere's diseases are the commonest causes of vertigo. Other causes include vertebrobasilar insufficiency, migraine, multiple sclerosis and cerebellar neoplasms.

Keywords

Vertigo · Migraine · vertebrobasilar insufficiency · vestibular neuronitis · benign positional vertigo

Introduction

The overall incidence of dizziness, vertigo and imbalance is 5–10% and reaches 40% in patients over the age of 40 years [1]. It is a common symptom in at least one-third of the patients over the age of 65 years [2]. One-year prevalence was 48.3% for vertigo, 39.1% for unsteadiness and 35.6% for dizziness [3]. Vertigo accounts for 52% of all cases [4, 5] and up to 56.4% in the elderly [6]. Overall prevalence in a rural community was 0.17% [7]. The prevalence of vertigo secondary to cardiovascular disease was 0.32%,

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_82

for neurological disease 0.14% and otologic disease 0.08% in a study of vertigo in an adult rural population [7]. In a study of 187 Chinese patients with vertigo, posterior circulation ischaemia was 59.8% followed by BPPV with 16.04%, and less affected were migraine, Meniere's disease and vestibular neuronitis, among others [8]. Epidemiological studies indicated that a quarter of the dizziness were central, and the most common central causes were cerebrovascular disease, migraine, multiple sclerosis and tumours of the posterior fossa [9] (Table 1).

Causes of Vertigo

Benign positional vertigo, vestibular neuronitis and Meniere's diseases are the commonest causes of vertigo. Other causes include vertebrobasilar insufficiency, migraine, multiple sclerosis and cerebellar neoplasms [10].

Benign Positional Paroxysmal Vertigo (BPPV)

BPPV is a common cause of vertigo in the elderly and becomes more frequent as age advances [11] and is most prevalent in those above the age of 50 years [12]. It is most common among peripheral vestibular disorders [13]. About 9% of a group of urban-dwelling elderly were found to have undiagnosed BPPV [14]. It is nearly always a benign condition [15]. BPPV causes nausea, vertigo, light-headedness and imbalance brought about by change in the position of the head [16], for instance, turning over in bed or getting out of bed. Tipping the head backwards as to reach for the upper shelf may precipitate it. Symptoms can be subjective or objective [12].

Degeneration of the vestibular system is the most common cause. Two basic theories of the pathology in BPPV are cupololithiasis and canalithiasis [17]. Other causes are infection,

Table 1 Guidelines for the differential diagnosis of vertigo [16, 23]

	Vestibular neuronitis	Benign positional vertigo	Meniere's disease	Acoustic neuroma	Vertebrobasilar disease
Onset	Sudden	Sudden	Sudden	Insidious	Sudden
Severity	Severe	Severe	Severe	Mild-moderate	Moderate-severe
Quality	True Vertigo	True Vertigo	True Vertigo	Dizziness/unsteadiness	Dizziness/vertigo
Duration	7–10 days	<3 s	Few to 24 h	Unremitting	Lasts several minutes
Triggers	Virus infection	Certain head position			
Associated symptoms	Nausea and vomiting	Nausea and vomiting	Nausea and vomiting		Visceral sensations
Neurologic					
Nystagmus	+	+Direction fixed	During attacks	Occasional	0
Hearing loss	+	0	+ (worsening)	+	+
Tinnitus	0	0	+	+	Drop attacks, diplopia, visual field deficits
Long tracts	0	0	0	V nerve, VII compression of the brain stem and cerebellum	
Progression	Self-limiting	Subsides	Subsides	Progresses	

head injury, minor strokes involving the anterior inferior cerebellar artery and medications such as gentamicin [18], but in more than half of the cases, the cause is unknown. Small crystals of calcium carbonate (otoconia), derived from the utricle as the result of damage to the utricle by injury, infection or degeneration because of advancing age, migrate into the canal system.

The history of vertigo or dizziness brought on by lying down or rolling over in bed together with the physical findings and auditory and vestibular tests helps in the diagnosis. The only diagnostic test that confirms the diagnosis of BPPV is Dix-Hallpike manoeuvre [16]. The individual is brought from a sitting position to the supine with the head turned 45° to the side and extended about 20° backwards. A positive response would be after a short latent period; there is a burst of rotating nystagmus. When the individual is brought up to the sitting position, there will be a reversal of the nystagmus. Fatigue of the nystagmus occurs when the procedure is repeated. Electronystagmography (ENG) may be needed to look for the character of the nystagmus induced by this manoeuvre. The vertigo is intermittent and is self-limiting and usually subsides in about 2 months but could last longer. The Epley manoeuvre and the Semont manoeuvre are intended to move the otoconia out of the sensitive part of the ear to less sensitive location with a cure rate of approximately 80% [19]. Positional restriction after canalith reposition manoeuvres for BPPV has been shown to be of no proven benefit [20].

Vestibular Neuronitis

Vestibular neuronitis is a benign disorder characterized by sudden onset of severe vertigo with nausea and vomiting and ataxia [21]. Hearing loss (unilateral) may be present [16]. It is often preceded by a viral illness which may be subclinical and all common viruses have been implicated. The virus selectively affects the inner ear neurosensory structures. Gradual resolution occurs over few days and complete recovery within 3 months. The elderly however could have exacerbations, usually less severe, and the conditions may be recurrent. Treatment is symptomatic with stabilizing measures and vestibular suppressant medication and rehabilitation exercises [22].

Meniere's Disease

Meniere's disease commonly presents in the 40–69 years of age. It is caused by idiopathic endolymphatic hydrops causing swelling of the semicircular ducts and damaging the hair cells. There is fluctuating hearing loss, tinnitus with vertigo and aural fullness and pressure [23]. Vertiginous episodes are paroxysmal lasting minutes to hours and decrease in frequency after multiple attacks only to recur months or years later, eventually with the hearing loss becoming permanent. The first line of treatment is medical which includes a low-salt diet, diuretic (thiazide) [18] and a betahistine, although the efficacies of these treatments have not been proven [24, 25]. Surgical treatment includes labyrinthectomy, vestibular nerve section, endolymphatic sac surgery and chemical ablation using intratympanic gentamicin in patients who have failed medical treatment.

Vertebrobasilar Insufficiency

Abrupt onset with nausea and vomiting and vertigo is the initial symptom in half of the cases. Other symptoms include drop attacks, diplopia, visual hallucinations and visual field defects in conjunction with dysarthria, dysphagia, sensory loss and hemiparesis. It rarely causes isolated vertigo attacks [26]. In impending infarction in the territory of the anterior inferior cerebellar artery, a transient vertigo may be the initial and only complaint. The risk of cerebral infarction following a vertebrobasilar TIA is much less than in the carotid circulation.

Acoustic Neuroma

Acoustic neuroma comprises about 90% of all cerebellopontine angle tumours. It arises from the eight nerves and is retrocochlear in location.

The symptoms begin insidiously with mild hearing loss, tinnitus, vague dizziness, disturbance of balance and asymmetric hearing loss. In a small number of patients, the onset is sudden [27]. The cranial nerves, facial and trigeminal (diminished corneal reflex), may be involved by the tumour extending in the cerebellopontine angle, and brain stem compression may occur if untreated. Bilateral acoustic tumours are rare except in patients with neurofibromatosis.

Multiple Sclerosis

Multiple sclerosis is an important cause of central vertigo. Because of the transient nature of these attacks, days to weeks [16], it may be mistaken for one of the self-limiting peripheral causes of vertigo such as vestibular neuronitis [16]. The patients affected are younger than those with benign positional vertigo. The first symptom is often an acute optic neuritis with loss of central vision in one eye, which in most instances resolves. Involvement of the brain stem may produce double vision, dizziness, cerebellar ataxia, dysarthria, dysphagia, numbness of one side of the face and an unsteady gait.

Migraine-Associated Vertigo

This is an atypical form of aura and the dizziness antedates the headache. Individuals with basilar migraine may complain of recurring headaches associated with visual aura followed by vertigo, dysarthria, tinnitus, visual disturbances and unsteadiness in walking [16]. At times, there may be no headache, making the diagnosis difficult. Dietary changes and tricyclic antidepressant generally improve vertiginous migraine headaches [22].

Evaluation

The evaluation of vertigo involves (1) medical history including a drug history, (2) physical examination, (3) laboratory evaluation, (4) vestibular function tests and (5) other diagnostic tests as needed. The medical history is important since the description of each symptom together with the duration and precipitating factors is crucial in establishing the diagnosis. In more than three-quarters of the cases of vertigo, the diagnosis can be made on the history alone. Recurrent vertigo is more suggestive of BPPV, Meniere's disease or migraine, whereas a single attack lasting for days or more is due either to cerebellar infarction or vestibular neuronitis [26]. Physical examination would include examination of the ear and a neurological examination.

If the patient has true vertigo, the task is one of determining whether it is central or peripheral. Box 1 shows some of the distinguishing characteristics of central and peripheral vertigo [16, 28]. Evidence of brain stem symptoms rules out a peripheral lesion. However, the absence of brain stem symptoms does not exclude a central lesion. Multiple sclerosis and vertebrobasilar insufficiency presenting with isolated vertigo evolve gradually, and the diagnosis may not be apparent at the time of initial presentation. In one study, seven patients had sudden bilateral hearing loss, tinnitus and vertigo, and the initial diagnosis was acute labyrinthitis or Meniere's disease, until the other brain stem and cerebellar signs appeared [29]. In multiple sclerosis, there are recurrent episodes, with remissions, and in the case of vertebrobasilar insufficiency, prior history of cerebrovascular disease or cardiovascular disease will be helpful in making the distinction. Episodes of vertigo, hearing loss and tinnitus associated with Meniere's disease can mimic those of acoustic neuroma, and the distinction between them before the appearance of brain stem symptoms can be difficult. The hearing loss with acoustic neuroma however is steadily progressive, whereas it is fluctuating or episodic with Meniere's disease. Triggering factors and duration of the attacks can help in determining the peripheral causes of the vertigo. In BPPV, the vertigo is with changes in the position of the head and neck, lasts only a few minutes and is recurrent daily. A single severe episode of vertigo after a viral illness is usually due to vestibular neuronitis.

Neurological and audiological testing can be helpful in making the distinction. Routine

Box 1 Some Characteristics of Peripheral Vertigo and Central Vertigo

Symptoms and signs	Peripheral	Central
Severity	Severe	Less severe
Nystagmus	Always present	Less often
	Horizontal	Multidirectional
	Plane, usually	Pure vertical
	Mixed[a]	
Hearing	Common	Rare
Tinnitus	May occur	Rare
Vomiting/ nausea	Virtually always	Less frequent
	Present and severe	
Neurological	Rare	Common

Information sources: Chan [16] and Eggenberger and Lovell [28]
[a]Horizontal and rotational

laboratory tests would include a full blood count, sedimentation rate and thyroid function tests, among others. The Dix-Hallpike manoeuvre should be done if the history is suggestive of benign positional vertigo or if the nystagmus is inducible. Vestibular function tests are the Dix-Hallpike manoeuvre, electronystagmography and the rotational chair testing. Audiometry, electronystagmography and brain stem evoked potentials are most useful. The sensitivity of brain stem evoked auditory potentials to detect retrocochlear lesions for acoustic tumours >2 cm is 100% as with MRI [30]. The MRI is used to exclude retrocochlear pathology. To ensure the diagnosis of acoustic neuroma, T1-weighted magnetic resonance imaging with gadolinium (Gd-DTPA) is the gold standard [31], is sensitive and will detect extremely small tumours of 2 mm in size. This technique also identifies other intracranial tumours, meningiomas and demyelinating lesions in the central nervous system. More recently, MR protocols have been used for fast-spin-echo (FSE) imaging [31, 32] for internal auditory canal structures and do not require contrast medium. Three-dimensional fast imaging employing steady-state acquisition (3D-FIESTA) MRI is a sensitive method for the diagnosis of cochlear or retrocochlear lesions and is useful as a screening tool in patients with unilateral ear symptoms [33]. CT scan may be used for inner ear pathology when MRI is not available or when MRI is contraindicated or when tumours more than 1.5 cm in diameter are excluded. Acoustic neuromas are isodense with the brain tissue and intravenous contrast enhancement should be used.

Impact

Dizziness is common in medical practice and is known to impair the health-related quality of life (HR-QoL) [34–36]. It affects daily functioning and is associated with functional disability, falls,

Box 2 Key Points: Vertigo

Epidemiological studies indicated that a quarter of the dizziness were central, and the most common central causes were cerebrovascular disease, migraine, multiple sclerosis and tumours of the posterior fossa [9].

BPPV is a common cause of vertigo in the elderly and becomes more frequent as age advances [11].

The only diagnostic test that confirms the diagnosis of BPPV is Dix-Hallpike manoeuvre [16].

In Meniere's disease, there is fluctuating hearing loss, tinnitus with vertigo and aural fullness and pressure [23].

Vertebrobasilar insufficiency rarely causes isolated vertigo attacks [26].

In a small number of patients with acoustic neuroma, the onset was found to be sudden [27].

Multiple sclerosis is an important cause of central vertigo.

Dietary changes and tricyclic antidepressant generally improve vertiginous migraine headaches [21].

social isolation and institutionalization [37, 38]. In a study to determine the impact of dizziness and balance disorders in persons >65 years old, balance problems were seen to be associated with unsteadiness, vertigo and faintness and difficulty in walking on uneven surfaces [39]. Approximately in one in five patients, medication triggered the balance problem [39] (Box 2).

Multiple Choice Questions

1. The following relating to vertigo are correct except:
   A. Benign positional paroxysmal vertigo (BPPV) is a common cause of vertigo in the elderly and becomes more frequent as age advances.
   B. Meniere's disease eventually results in permanent deafness.
   C. A transient vertigo may be the only complaint in impending infarction in the territory of the anterior cerebellar artery.
   D. Migraine-related vertigo is always accompanied by headache.
2. The following are true in relation to the different causes of vertigo except:
   A. The only diagnostic test that confirms the diagnosis of benign paroxysmal positional vertigo (BPPV) is Dix-Hallpike manoeuvre.
   B. The Epley and the Semont manoeuvres have a cure rate of approximately 80% in patients with BPPV.
   C. The MRI is used to exclude retrocochlear pathology.
   D. Bilateral acoustic neuromas are common.
3. The following symptomatology in relation to causes of vertigo are true except:
   A. In BPPV, the vertigo is with changes in the position of the head and neck and lasts for several hours and is not recurrent.
   B. A single severe episode of vertigo after a viral illness is usually due to vestibular neuronitis.
   C. In Meniere's disease, the hearing loss is fluctuating and episodic.
   D. The hearing loss in acoustic neuroma is steadily progressive.

MCQ Answers

1 = D; 2 =D; 3 = A

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Tinnitus

83

Contents

Abstract

Tinnitus is common in the elderly, and its prevalence increases with age. In the elderly, it is most commonly associated with hearing loss. The exact underlying cause of tinnitus is not fully understood. The evaluation of tinnitus follows similar lines to that of hearing loss. Modifiable factors that may exacerbate tinnitus should be identified and treated accordingly, for instance, certain medications such as aspirin, NSAIDs and quinine, and ceasing the drug may be reasonable. The chapter reviews the causes and evaluation management of tinnitus.

Keywords

Tinnitus · Subjective tinnitus · Objective tinnitus · Behavioural and combined therapies · Tinnitus retraining therapy

Introduction

Tinnitus is characterized by the perception of sound in the ears or in the head. Prevalence estimates of persons with tinnitus vary widely from 7.9 million [1] to more than 37 million [2]. Many individuals will experience transient tinnitus lasting for less than 5 min that may not compel them to seek medical evaluation [3], but 10–15% of adults have prolonged tinnitus necessitating medical evaluation [4]. Tinnitus is common in the elderly and its prevalence increases with age. In the elderly, it is most commonly associated with hearing loss [5].

Causes of Tinnitus

The exact underlying cause of tinnitus is not fully understood. Many of the causes of tinnitus result from an underlying disorder, and many result

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_81

Table 1 Causes of subjective tinnitus

Subjective tinnitus (audible only to the individual)	
Unilateral	Bilateral
i. External aural disorders, e.g. cerumen impaction, foreign body	i. Presbycusis
	ii. Chronic noise exposure
ii. Middle ear disorders, e.g. otitis media otosclerosis, neoplasms	iii. Metabolic disorders
	iv. Autoimmune disorders
iii. Inner ear-cochlear sudden onset – viral, microvascular	v. Ototoxic medications
	vi. Mental illness – depression anxiety
iv. With vertigo, hearing loss – Meniere's disease	vii. Idiopathic
v. Hearing loss, disequilibrium focal neurological signs – acoustic neuroma	viii. Systemic diseases – syphilis meningitis, arachnoiditis

Information sources: Richmond [3], Benson et al. [5] and Deitz et al. [6]

Table 2 Causes of objective tinnitus

Objective tinnitus (audible to anyone)	
Vascular (pulsatile)	Non-vascular
i. Carotid artery stenosis, ectatic, aberrant intratympanic carotid artery	i. Degenerative diseases, e.g. ALS
ii. Jugular vein and bulb-dehiscent bulb, venous hum, glomus tumour	ii. Myoclonus or flutter of stapedius or tensor tympani and lysis of the muscles after tympanectomy incision
iii. Metabolic disorders with haemodynamic impact, e.g. anaemia, thyroid dysfunction	iii. Eustachian tube dysfunction, patulous
iv. Vascular neoplasms	iv. Middle ear effusion
v. AV malformations, aneurysms	v. Palatal myoclonus due to lesion brainstem lesion – stroke, trauma, multiple sclerosis, encephalitis, degenerative disorders
vi. Focal stenosis of lateral sinus	vi. TMJ dysfunction (Costen's syndrome)
	vii. Benign intracranial hypertension

Information sources: Richmond [3], Benson et al. [5] and Deitz et al. [6]

from the same conditions causing hearing loss (Tables 1 and 2).

Evaluation of Tinnitus

The evaluation of tinnitus follows similar lines to that of hearing loss. The diagnosis and recognition of the underlying cause, associated disease or modifiable factors are meaningful as treatment of the underlying cause may relieve the tinnitus symptoms. Distinguishing subjective, objective, laterality (unilateral or bilateral), symmetry, pulsatile or non-pulsatile may be valuable. A thorough history including the past history, physical examination and laboratory tests is indicated. Specialized tests include audiogram, evoked response audiometry especially in individuals with unilateral tinnitus and imaging, X-rays, CT and MRI. Furthermore, other tests that measure the specific features of tinnitus itself [7] are the following:

Tinnitus pitch test: From a group of external tones or noises, the individual selects the pitch of the tinnitus which closely matches his tinnitus.

Tinnitus loudness test: by adjusting the loudness of an external tone that matches the loudness of the tinnitus.

Mask ability of tinnitus: measures the degree to which the tinnitus may be masked by other external sounds.

Residual inhibition: following a period of masking the amount of time taken for the noise in the ear to be eliminated or reduced [7].

Treatment

Modifiable factors that may exacerbate tinnitus should be identified and treated accordingly, for instance, certain medications such as aspirin, NSAIDs and quinine, and ceasing the drug may be reasonable. In some alcohol, caffeine and smoking may increase tinnitus [3]. Elevated stress, poor sleep hygiene and coexisting illnesses are identified and treated [3]. External sound has been used for the management of tinnitus in different capacities in a manner that gives the most benefit [8, 9]. Night-time playing background music to mask the tinnitus, the so-called white

noise, may give some relief and help the person to fall asleep. In some, the use of a hearing aid or tinnitus 'masker' may help to suppress the tinnitus. This is a device like the hearing aid that produces pleasant sounds. A wide variety of drugs have been tried, including antidepressants, neuromodulators, vasodilators and nicotinic acid, but none have been shown to be more effective than a placebo. For the profoundly deaf, cochlear implants may reduce the tinnitus. Behavioural and combined therapies such as hypnosis, cognitive therapy, biofeeding training, relaxation techniques, meditation and yoga have shown some benefit in some individuals. Tinnitus retraining therapy has found some success in reducing severe tinnitus perception [3].

Impact

Tinnitus diminishes the health and well-being in the elderly and may be associated with functional difficulties, depression, anxiety [10], sleep difficulties [11] and emotional balance [12] amongst others. Comorbid psychiatric disorders are frequent in patients with tinnitus [13] and commonly present with neuropsychiatric symptoms [10]. Tinnitus in the elderly may have a negative effect on the quality of life [12]. It may affect activities of daily living and instrumental activities of daily living [14]. It has been reported that it often accompanies presbycusis and may be more troublesome than deafness [15] (Box 1).

Box 1 Key Points: Tinnitus

In the elderly, it is most commonly associated with hearing loss.

Tinnitus is common in the elderly and its prevalence increases with age.

Distinguishing subjective, objective, laterality (unilateral or bilateral), symmetry, pulsatile or non-pulsatile may be valuable.

Specialized tests include audiogram, evoked response audiometry especially in individuals with unilateral tinnitus and imaging, X-rays, CT and MRI. Furthermore, other tests measure the specific features of tinnitus itself [7].

Pulsatile tinnitus requires investigation of the cardiovascular system.

Any indication of an acoustic neuroma, glomus tumour or cerebrovascular pathology requires referral to the otolaryngologist.

In some alcohol, caffeine and smoking may increase tinnitus [3].

Multiple Choice Questions

1. The following statements in relation to tinnitus are true except:
   A. Many causes of tinnitus may result from the same conditions causing hearing loss.
   B. In some alcohol, caffeine and smoking may decrease tinnitus.
   C. Anti-depressants, vasodilators, neuromodulators and nicotinic acid are no better than placebo.
   D. The so-called white noise (night-time playing background music) helps to mask the tinnitus and gives some relief.

MCQ Answers

1 = B

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Part XIX

Visual Problems in the Elderly

Low or loss of vision can have negative consequences for elderly patients. It greatly affects the health and well-being, changes their ability to perform everyday activities and their ability to drive, and causes problems with walking and increasing the risk of falls. Part XIX provides information on the four causes of loss vision that are common to this population, namely (1) age-related macular degeneration (AMD), (2) glaucoma, (3) cataract, and (4) diabetic retinopathy (DR). This review also provides an overview of the prevalence and highlights the advances that have occurred in their clinical management. About 80% of legally blind Australians 50 years and older suffer from AMD. The lifetime risk is 50% in those with a relative with AMD as compared with 12% who do not have a relative. Once the AMD reaches the advanced stage, no form of treatment can prevent vision loss. More than 70 million people are affected worldwide with glaucoma with about 10% bilaterally blind. The WHO in 1990 estimated of the 38 million blind people in the world, cataract accounted for 41.8%. The beneficial effects of two types of drugs (fenofibrate and candesartan) on diabetic retinopathy have been publicized. Anti-angiogenic agents (anti-vascular endothelial growth factor) have been found to be effective in the treatment of DR and DME.

Loss/Low Vision

84

Contents

Abstract

The four common causes of low vision in the elderly patients are age-related macular degeneration, glaucoma, cataract and diabetic retinopathy. Three million Americans 40 years and older are affected by blindness or low vision, and by 2020, the projected number will be 5.5 million. About 80% of legally blind Australians 50 years and older suffer from age-related macular degeneration. This chapter will provide an update on the four important causes of visual impairment and their management.

Keywords

Age-related macular degeneration (AMD) · Glaucoma · Cataract · Diabetic retinopathy

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_95

Age-Related Macular Degeneration

Introduction

The four common causes of low vision in the elderly patients are (1) age-related macular degeneration (AMD), (2) glaucoma, (3) cataract and (4) diabetic retinopathy (DR) [1, 2]. In the industrialised nations, AMD and DR are the major contributing causes for visual impairment [3], and AMD is the leading cause among the elderly [4]. By the age of 65 years, one in three will have some form of visual-reducing eye disease [5]. Three million Americans 40 years and older are affected by blindness or low vision, and by 2020, the projected number will be 5.5 million [1].

About 80% of legally blind Australians 50 years and older suffer from AMD [6]. The end-stage-related AMD is found in 1.7% of all people over the age of 50 years, and the incidence increases to 0.7–10.4% in people aged 65–75 and to 11–18.5% in those above the age of 85 years [7–9]. Women are more at risk than men. Whites are more likely to be affected by AMD than African Americans [10]. Genetic variation at two major loci on chromosomes 1 and 10 is associated with AMD [11]. Those with a history of immediate family members with AMD are at higher risk. The lifetime risk is 50% in those with a relative with AMD as compared with 12% who do not have a relative with macular degeneration [12]. Other factors include tobacco smoking, sunlight exposure and nutritional factors. Smoking is the only proven modifiable risk factor [13, 14] and has been associated with both dry and wet forms of AMD [4]. Cataract surgery and family history of AMD are concomitant risk factors of AMD [14].

Soft drusen are found in 13.3% of people, with distinct drusen more frequent than indistinct soft drusen, and retinal pigmentary abnormalities are seen in 12.6% and are more frequent in males [8]. Apart from lipofuscin, lipoproteins and amyloid beta accumulate under the retinal pigmentary epithelium (RPE), and these deposits are called basal laminar deposits (BLamD), and the early forms are considered a part of normal ageing [15]. In AMD they are thicker and hyalinised and appear as pigmentary changes [16]. At the level of the Bruch membrane, there are linear deposits (BLinD) [15], and the clinical correlation of confluent areas with BLinD is soft drusen [11]. Dysfunction of the RPE occurs early and is brought about by an inherited susceptibility and/or environmental exposure [17]. Extracellular matrix (ECM) material is produced by the RPE and plays an important role in some of the functions of this tissue.

Hard drusen are small and occur in clusters and are globular in shape and pose a low rate of choroidal neovascularisation (CNV) (Fig. 1). The soft drusen are larger and tend to be confluent and precede to drusen-related geographic atrophy [11] (Fig. 2) or to the development of RPE detachment and choroidal neovascularisations (CNVs) [18] and are specific for AMD. The late stage has two forms, atrophic (or dry) characterised by geographical atrophy (age-related maculopathy) and

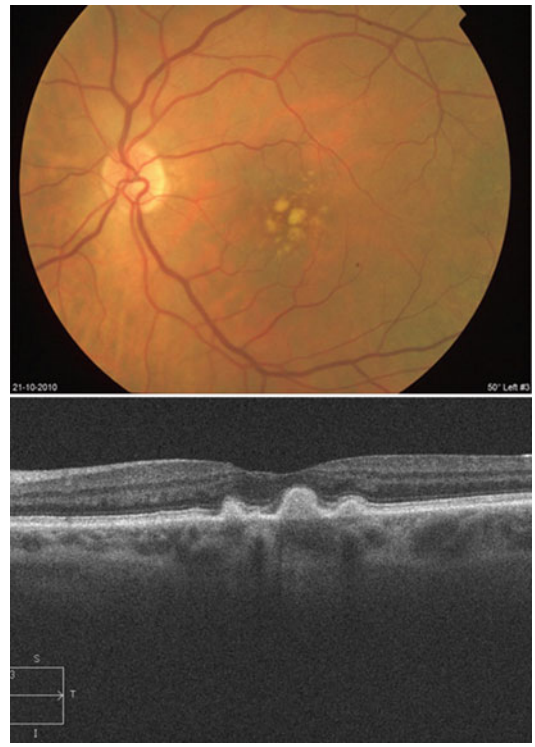

Fig. 1 Hard drusen with OCT (Reproduced, with kind permission, from Dr. John Sarks)

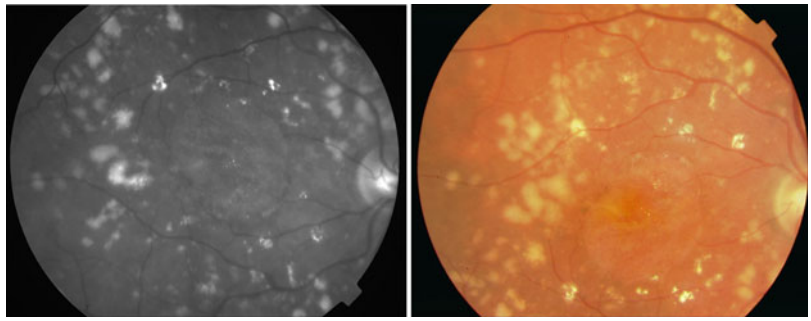

Fig. 2 Geographic atrophy, *red*-free and colour (type of dry ARMD). The circular area in the centre is the area of pigment epithelial atrophy. There are numerous drusens. Some pigment clumping at 10 o'clock (Published, with kind permission, from Associate Professor WM Amoaku, University of Nottingham)

exudative (wet) characterised by development of choroidal neovascularisation (CNV). The new vessels that are formed are abnormal and could leak fluid and blood into the macular giving rise to macular oedema (Fig. 3). Mostly geographical atrophy occurs in areas of regressed large drusen [19]. Figure 4 shows geographical atrophy as a well-defined confluent atrophy of the retinal pigment epithelium in a patient with diabetic retinopathy.

Clinical Manifestations

In those diagnosed with AMD, atrophy accounts for less than 25% of the cases, and 90% have the dry atrophic type. Atrophic type may be the end result and is seen in patients over the age of 80 years unless CNV develops [6]. If CNV develops abruptly, it may hasten the loss of vision and accounts for more than 85% of patients with severe vision loss [6]. There is blurring of vision which is usually of gradual onset except in those with exudative macular degeneration. The vision may be distorted (metamorphopsia) [20], and straight lines may appear wavy, and the venetian blind may appear to bulge in the centre, and those at high risk should be given the grid of fine lines to view. There is loss of discriminating colours, and central vision is distorted with missing areas – central scotoma [20]. There is difficulty in seeing objects, reading, sewing and other daily tasks; however the peripheral vision is preserved to a variable extent. Visual acuity decreases as the disease progresses. Exudative changes occur and include white hard exudates, intraretinal haemorrhages, subretinal and sub-RPE and the presence of intraretinal fluid. There are pigmentary alterations, and in the late stages, disciform scar tissue [20] and large abnormal vessels and retinal folds are seen.

Investigations

The Amsler grid is a simple and effective way for patients to monitor the retina. Fluorescein angiography (FA) allows identification and localisation of abnormal vascular processes and confirms and localises the presence of CNV (Fig. 5), and several angiographic patterns have been described for CNV [20]. Ophthalmic coherence tomography (OCT) analogous to ultrasound is a useful imaging technique to diagnose and manage a variety of retinal diseases and glaucoma [21]. It depicts the layers of the retina and the underlying RPE. The axial resolution is 10–100 times better than MRI or ultrasound. It can identify soft drusen, RPE detachments, CNV, macular oedema and intraretinal fluid. Drusen appear as focal RPE deformations [11] (Fig. 6a, b). Presently it is the imaging modality of choice in the management of CNV; however OCT cannot totally replace FA in the management of CNV [20].

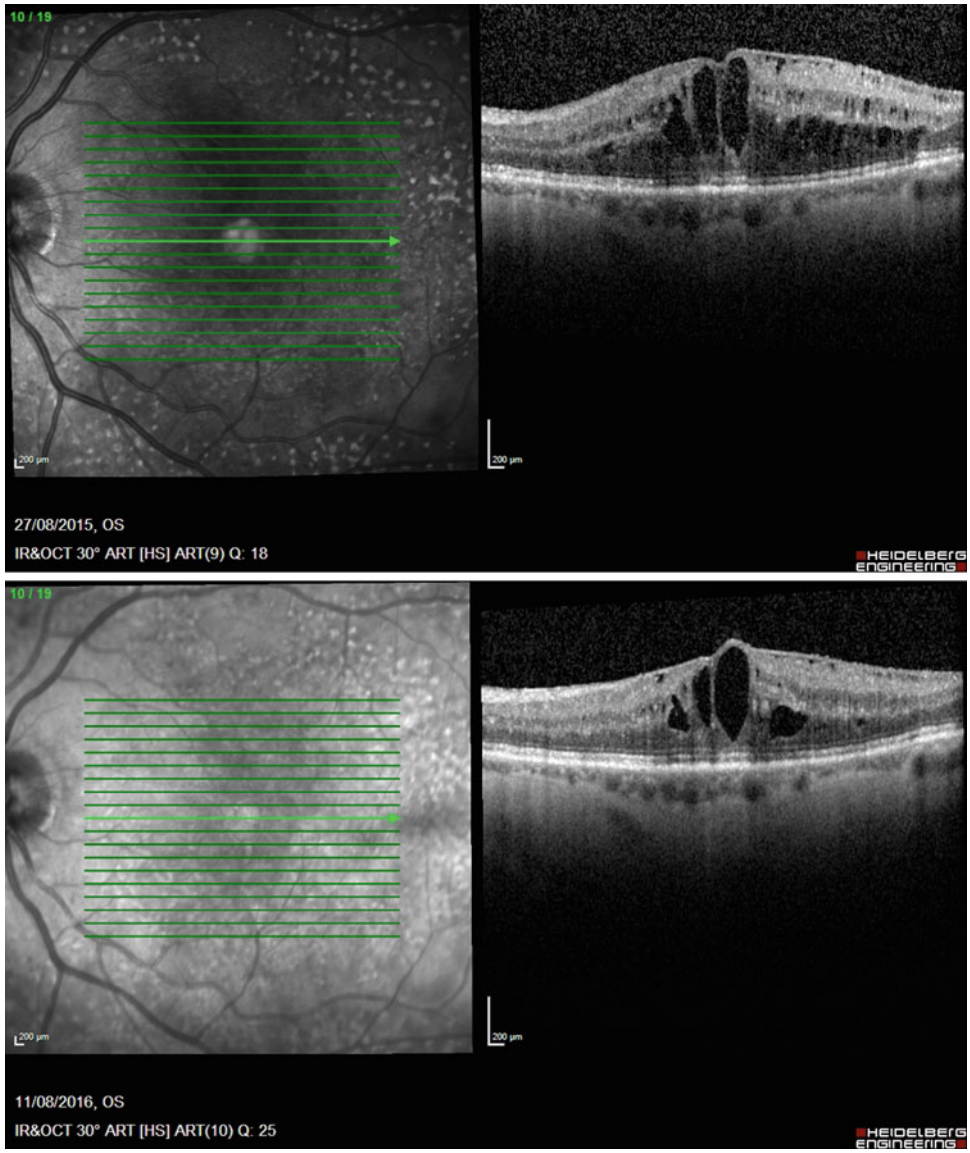

Fig. 3 The optical coherence tomography of macular oedema 1 year apart. The *dark* areas are the oedematous spaces. This is a cut along the *green arrow*. The deeper layers of the retina flat compared with the images of drusen (Published, with kind permission, from Associate Professor, WM Amoaku, University of Nottingham)

Treatment

The treatments include (i) anti-VEGF therapy, (ii) laser surgery, (iii) photodynamic therapy and (iv) vitamin therapy. For dry AMD patients, the requisite advice is to cease smoking, avoid ultraviolet and blue light and emphasise the importance of healthy diet and potential value of nutritional supplements [22]. The Age-Related Eye Disease Study (AREDS) had demonstrated that taking of a specific high-dose formulation of antioxidants significantly reduces the risk of advanced AMD and its associated vision loss [10]. The AREDS formulation consists of 500 mg of vitamin C, 400 IU of vitamin E,

15 mg of beta-carotene equivalent to 25,000 IU of vitamin A, 80 mg of zinc and 2 mg of copper as cupric oxide [23]. The retina consists of zeaxanthin, lutein and carotenoids which protect the retina from blue light damage. Subsequent to the AREDS, the Lutein Antioxidant Supplementation Trial (LAST) demonstrated that taking 10 mg lutein daily with or without additional antioxidants improved visual function [24]. Lutein and zeaxanthin are found in dark green leafy vegetables. The amount of lutein absorbed from foods (eggs, spinach, lettuce, broccoli, zucchini, corn, peas and Brussels sprouts) and supplement surveys indicate that the average intake may be below that are associated with disease prevention [24, 25]. Lifestyle changes can play a role in reducing the risk of developing AMD which includes a healthy diet high in leafy vegetables and fish, smoking cessation, blood pressure and weight control and increased physical activity [23].

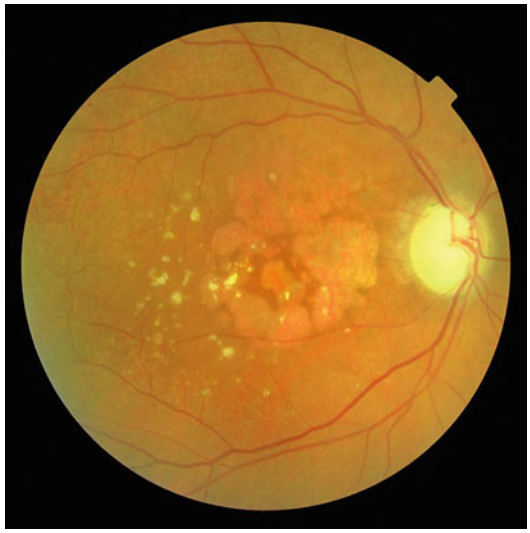

Fig. 4 Non-neovascular age-related macular degeneration (geographic atrophy) in a diabetic patient with diabetic retinopathy shows as a well-demarcated confluent atrophy of the retinal pigment epithelium (Reproduced, with kind permission, from Dr. P. Nithianandan)

Once the AMD reaches the advanced stage, no form of treatment can prevent vision loss. Laser and photodynamic therapy are now used rarely, the treatment for CNV having been revolutionised by anti-VEGF therapy. Options for the management of wet AMD include argon laser (extrafoveal CNV) photocoagulation, photodynamic therapy (subfoveal and juxtafoveal CNV) and VEGF inhibitors (for any lesion type or location) [22, 26]. Well-defined extrafoveal CNV treated with photocoagulation has shown a reduction in severe visual loss [14], but such lesions represent only

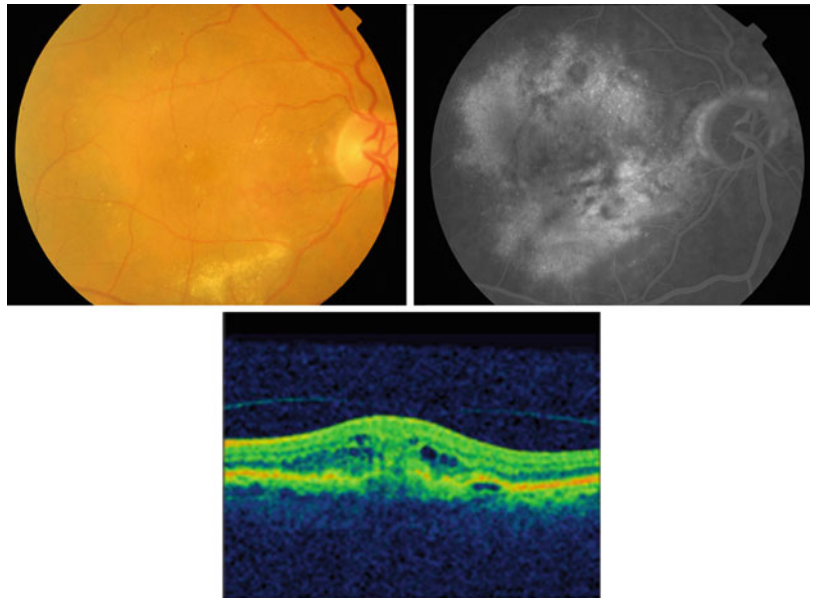

Fig. 5 Wet AMD and FFA showing the diffuse leakage (large occult CNV – choroidal neovascular membrane). The optical coherence tomography (*below*) shows the disruption to the retinal pigment epithelium (*red layer below*), retinal oedema and blood (the spaces in the retina) (Published with the kind permission from Associate Professor WM Amoaku, University of Nottingham)

Fig. 6 (**a**) The optical coherence tomography. Note the unevenness of the retinal layers compared with the normal below which has a smooth contour. Disc and optic nerve is on the *left*. Macula is the depression in the centre. Retinal pigment epithelium is uneven *red line* and drusen distorting it (Published, with kind permission, from Associate Professor WM Amoaku University of Nottingham). (**b**) Normal optical coherence tomography. The smooth *thin white line* in the retinal slice is the retinal pigment epithelium, macula the central depression and the disc and optic nerve head at the right end (Published, with kind permission, from Associate Professor WM Amoaku, University of Nottingham)

8% of all CNV [3]. VEGF has been identified to promote the progression of CNV, and there are now four treatments that inhibit VEGF, pegaptanib (Macugen), bevacizumab (Avastin) and ranibizumab (Lucentis) [22] and aflibercept (Eylea). They are all delivered by trans-scleral injection into the vitreous cavity [22]. The anti-VEGF therapies are immensely useful for they can be used in all types of CNV [22]. The effectiveness and safety of ranibizumab for neovascular AMD have been shown in two clinical trials [27, 28]. Side effects are known to occur sometimes such as myocardial infarction and stroke. There is no firm decision as to the optimal or safe interval between two successive injections. Different trials have reported varying results. VEGF inhibitors are widely used in the vast majority of cases with wet form of ARMD. They are also used in retinal vein occlusion both central vein as well as branch vein occlusions and have been found useful in diabetic maculopathy. The main disadvantages are the need for repeated intravitreal injections, high cost and the requirement of treatment for 2 years or more [22] (Box 1).

Box 1 Key Points: Age-Related Macular Degeneration

About 80% of legally blind Australians in the 50 years and older suffer from AMD [6].

Age is a major factor. Women are more at risk than men. Whites are more likely to be affected by AMD than African Americans [10].

The lifetime risk is 50% in those with relative with AMD as compared with 12% who do not have a relative with macular degeneration [12].

Atrophic type may be the end result and is seen in patients over the age of 80 years unless CNV develops [6].

If CNV develops abruptly, it may hasten the loss of vision and accounts for more than 85% of patients with severe vision loss [6].

For dry AMD patients, the requisite advice is to cease smoking, avoid ultraviolet and blue light and emphasise on the importance of healthy diet and potential value of nutritional supplements [22].

Once the AMD reaches the advanced stage, no form of treatment can prevent vision loss.

Options for the management of wet AMD include anti-VEGF therapy, argon laser (extrafoveal CNV) photocoagulation/photodynamic therapy (subfoveal and juxtafoveal CNV) and VEGF inhibitors (for any lesion type or location) [2, 26].

Glaucoma

Introduction

More than 70 million people are affected worldwide with glaucoma with about 10% bilaterally blind [29]. In the Blue Mountains Eye Study, the prevalence of glaucoma was 3%, and this means that there are 150,000 Australians afflicted with this disorder of which 75% are above the age of 70 years and this number will double in 30 years [30]. According to the Beaver Dam Eye Study, the prevalence increases with age, increasing from 0.9% in people 43–54 years to 4.7% in people 75 years and older, and there is no significant effect on sex after adjusting for age [31]. The prevalence of glaucoma in people 40 years and older in South India is found to be no lower than for white population [32].

In a small percent of cases, several putative genes have been isolated [33, 34]. The risk factors include age, family history [35], diabetes, hypertension, myopia, migraine and cardiovascular disease [36, 37], together with cataracts, tumours, eye surgery and injury. Age, females and Asian ethnicity are risk factors for angle-closure glaucoma [35]. High intraocular pressure appears to be an important risk factor [35] and for progression of glaucoma, but whether fluctuation of intraocular pressure and central corneal thickness are associated with progression is unclear [38]. Several population-based studies have shown that in about 25–50% with glaucoma, the intraocular pressure was lower than 22 mmHg [39, 40]. Furthermore, a significant number of people with raised intraocular pressure even when followed up over lengthy period never develop glaucoma [39].

Clinical Manifestations

Open-angle glaucoma is the most common of all glaucoma and usually affects both eyes. It is characterised by the pattern of visual field deficit, morphological loss of optic disc and increased intraocular pressure (IOP) [41]. It is a slowly progressive disorder. In the early stages, it is asymptomatic [42] until the disease is quite advanced [35, 42], and as the disease progresses with the loss of retinal ganglion axons, the peripheral vision is first lost. If the inferior visual fields are involved, the patients may complain of missing stairs or may have difficulty in driving or reduction in the ability to perform activities of daily living [35]. Central vision is last to be affected. In less than one-third of the patients with acute angle-closure glaucoma, the symptoms come on suddenly with severe eye pain, headache, halos around lights, decreased vision, nausea and

vomiting [35]. Examination of the patient reveals a dilated pupil, conjunctival injection, steamy cornea, lid oedema, lacrimation and very high intraocular pressure [35]. Like in the case of open-angle glaucoma, it can be asymptomatic until advanced vision loss has occurred [35].

Diagnosis

Diagnosis includes history and physical examination of the eye followed by ophthalmic examination, measurement of intraocular pressure by tonometry, visual acuity, visual fields, pupillary reflex response and slit-lamp examination. The cup-to-disc ratio is used to assess the progression of the glaucoma. Optical coherence tomography (OCT) is commonly used to evaluate glaucomatous damage. The increased intraocular pressure in glaucoma causes cupping of the disc (Fig. 7). The normal cup-to-disc ratio is 0.3. As the glaucoma advances, the cup enlarges (Fig. 8).

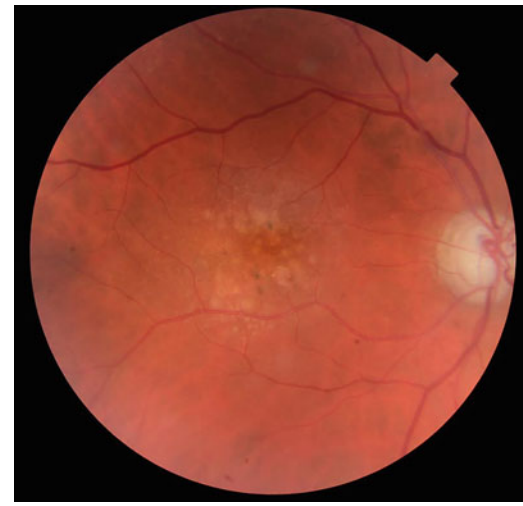

Fig. 7 Shows glaucoma with typical dry ARMD. The glaucomatous disc is cupped with a large cup/disc ratio. The small vessel just above the inf. temp. artery is dipping into the cup. Also shows patches of pigment epithelial atrophy and pigment clumping in areas consistent with dry ARMD (Published with the kind permission from Associate Professor WM Amoaku, University of Nottingham)

Treatment

In glaucoma there is progressive optic neuropathy including death of retinal ganglion cells and their axons leading to loss of visual field and characterises the pathology of open-angle glaucoma which is the most common form. The only proven method of treatment is lowering of the intraocular pressure [43]. The reduction of pressure can be achieved by either reducing the secretion of aqueous humour by the ciliary body or by enhancing aqueous outflow through the trabecular meshwork or alternative pathway. The treatments for open-angle glaucoma include eye drops, laser trabeculoplasty and incisional surgery used alone or in combination [44]. Usually topical drug therapy is used first. The intraocular pressure-reducing agents are shown in Table 1. Currently as the first line of choice, there has been a shift from beta-blockers to prostaglandin derivatives [45]. Laser or incisional surgeries are indicated when adequate reduction of intraocular pressure is not achieved by medical treatment [35]. In the case of acute primary angle-closure glaucoma which is a medical emergency, topical and systemic medications followed by iridotomy abort the attack in 42–72% of cases [35].

Cataract

Introduction

The WHO in 1990 estimated that of the 38 million blind people in the world, the cataract accounted for 41.8% [48]. Nuclear cataracts are associated with central lens opacification, corneal cataracts are characterised by radial spokes extending from the periphery and posterior subcapsular cataracts are situated in the posterior cortical layer [2]. Apart from ageing which is the most important risk factor [49, 50], changes in the lens could occur as the result of exposure to x-rays, ultraviolet light, heat from infrared exposure and other environmental influences. It occurs in diabetes, with smoking and alcohol, in patients with uveitis and poor nutrition and in those taking systemic medications like corticosteroids. Recent studies

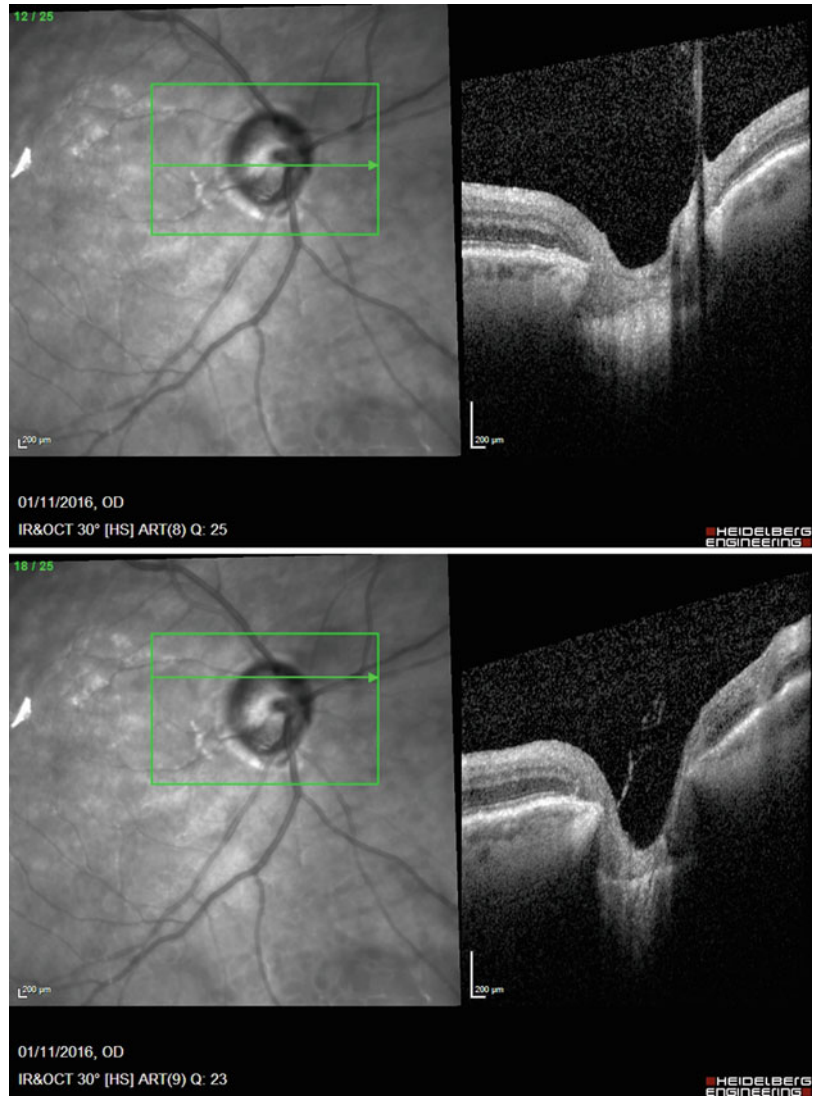

Fig. 8 The optical coherence tomography shows the disc cut at two levels to show depth of the cup in glaucoma. The cup/disc ratio is about 0.9 and is vertically cupped. The tiny inferior temporal vessel is dipping into the cup (Published with the kind permission from Associate Professor WM Amoaku, University of Nottingham)

have shown that women on hormone replacement therapy have a lower incidence compared to control cohort of the same age suggesting a hormonal influence in the development of cataract [51].

Clinical Manifestations

It is categorised according to location, namely, cortical, nuclear or posterior subcapsular. The amount of vision that is affected will depend on density and location of the cataract, for instance, the cataract in the area of the lens directly behind the pupil will affect the vision significantly. It usually presents with blurred vision gradual and painless and is progressive with the frequent need to change glasses. Changes in colour vision, increased glare from headlights at night while driving, day glare and the presence of a milky whiteness in the pupil occur as the cataract progresses.

Treatment

Surgery to remove the cataract is now an out-patient procedure, and a replacement lens is

Table 1 Medications in glaucoma, mode of action and their side effects

Medication	Mode of action	Side effects
Beta-adrenergic receptor antagonists	Reduces secretion of aqueous humour	Considered in the dd of confusional syndromes, COAD, cardiac failure in the elderly
Timolol	Non-cardioselective	Causes asthma (bronchospasm), allergic reactions, confusion, chest pain, cardiac arrhythmias
Carteolol	Non-cardioselective	Headache, dizziness, depression
Levobunolol	Non-cardioselective	Blurred vision, chest pain, confusion, dizziness
Betaxolol	Cardioselective	Dry eyes, blurred vision, sleep problems, muscle weakness
Carbonic anhydrase inhibitors	Reduces aqueous formation	Heartburn, fatigue, paraesthesia of extremities, metabolic acidosis
Acetazolamide (oral)		Rarely agranulocytosis, renal calculi or tubule calcification
Dorzolamide and brinzolamide (topical)		
Alpha-2-adrenergic agonists	Dual mechanism	Upper lid elevation, enlarged pupil, itching
Brimonidine	Decreases aqueous secretion	
Apraclonidine		
Dipivefrin	Increases aqueous outflow	
Parasympathomimetics	Increasing aqueous outflow	Causes miosis, exacerbate effects of cataract and ageing retinal function, frontal headaches Systemic – bronchospasm, pulmonary oedema, abdominal spasm, salivation
Pilocarpine		
Carbachol		
Cholinesterase inhibitors	Depresses pseudocholinesterase levels	Fever, local and systemic effects
Echothiophate		
Prostaglandin receptor agonists	Increasing uveoscleral outflow	Burning, stinging, curling of eyelashes
F2a-isopropyl ester (Xalatan, latanoprost)		
Prostamides		
Hyperosmotic agents	Moving fluid out of vitreous into blood	Glycerol – nausea, vomiting
Mannitol (IV)		Mannitol – cardiovascular overload, pulmonary oedema
Isosorbide (oral)		
Glycerol (oral)		

Information sources: Goldberg et al. [46], Maclean [47] and Quillen [2]

usually inserted. In intracapsular cataract extraction (ICCE), the lens and entire capsule are removed. There is an increased risk of retinal detachment and swelling following surgery. In extracapsular cataract extraction (ECCE) which is the most common form of surgery, the lens and front portion of the capsule are removed and the posterior part remains and the intraocular lens is placed in it. Phacoemulsification involving ultrasonic fragmentation of the lens followed by aspiration of the pieces is the technique used in cataract surgery today and a lens implanted either in the lens capsule or in front of the iris [2] (Boxes 2 and 3).

Box 2 Key Points: Glaucoma

The risk factors include age, family history, diabetes, hypertension, myopia, migraine and cardiovascular disease [36, 37], together with cataracts, tumours, eye surgery and injury.

The only proven method of treatment is lowering of the intraocular pressure [43].

(*continued*)

Box 2 Key Points: Glaucoma (continued)

Currently as the first line of choice, there has been a shift from beta-blockers to prostaglandin derivatives [45].

In less than one-third of the patients with acute angle-closure glaucoma, the symptoms come on suddenly with severe eye pain, headache, halos around lights, decreased vision, nausea and vomiting [35].

In the case of acute primary angle-closure glaucoma which is a medical emergency, topical and systemic medications followed by iridotomy may abort the attack in 42–72% of cases [35].

The general practitioner should view the optic disc with an ophthalmoscope from time to time especially in those with one or more risk factors.

Box 3 Key Points: Cataract

Cataract is characterised by opacity of the lens either developmental or degenerative.

Ageing by reducing the metabolic efficiency of the lens makes it more vulnerable to noxious factors leading to the formation of a variety of cataracts.

It is categorised according to location, namely, cortical, nuclear or posterior subcapsular.

Phacoemulsification involving ultrasonic fragmentation of the lens followed by aspiration of the pieces is the technique used in cataract surgery today [2].

Surgery to remove the cataract is now an out-patient procedure and a replacement lens is usually inserted.

Box 4 Key Points: Diabetic Retinopathy

Patients with DR usually complain of blurred vision, poor night vision, visual field loss and floaters [2].

Box 4 Key Points: Diabetic Retinopathy (continued)

Diabetic retinopathy is classically defined by its vascular lesions and classified as non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) [53].

The beneficial effects of two types of drugs (fenofibrate and candesartan) on diabetic retinopathy have been publicised [60, 61].

Antiangiogenic agents (anti-vascular endothelial growth factor) have been found to be effective in the treatment of DR and DME [59].

However repeated injections may increase local complications such as vitreous haemorrhage, retinal detachment and traumatic cataract [62].

Diabetic Retinopathy

Introduction

The prevalence of diabetic retinopathy (DR) increases with the duration of the disease and with age. About 86% of blindness in the younger-onset group is diabetic retinopathy, and in the older-onset group in which other eye diseases are common, it is one-third of the cases of legal blindness [52]. A number of biochemical pathways have been proposed as possible links between hyperglycaemia and DR [53]. There is a close association between chronic hyperglycaemia and development and progression of DR, but the underlying mechanism that leads to development of microvascular damage remains unclear [54] .

Clinical Manifestations

Patients with DR usually complain of blurred vision, poor night vision, visual field loss and floaters [2]. Diabetic retinopathy is classically

defined by its vascular lesions and classified as non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) [53]. NDPR is further subdivided into mild, moderate and severe [53]. NDPR is manifested by focal closure of retinal capillaries, microaneurysms and associated punctuate haemorrhages, serous exudates and, occasionally, cotton-wool spots secondary to acute ischaemia (Fig. 9). These changes rarely cause serious visual problems [55]. As the disease progresses, there is increased vasopermeability, resulting in retinal thickening (oedema) and lipid deposits (hard exudates) that may involve the centre of the macula or close to it [56]. The Early Treatment Diabetic Retinopathy Study (ETDRS) [57] introduced the term clinically significant macular oedema (CSME) to describe this state (Fig. 10). Further progression leads to gradual closure of the retinal vessels and with increasing ischaemia results in venous abnormalities such as dilatation, beading and loops with increasing haemorrhages and exudation [56] (Fig. 11). On the other hand, PDR is more threatening and involves the growth of new blood vessels on or near the disc (NVD) or elsewhere in the retina (NVE) [56] resulting in vitreous haemorrhage (Fig. 12a–c). There is concomitant fibroblastic activity resulting in traction bands, tears and retinal detachment [55, 56]. The new vessels can grow into the iris resulting in neovascular glaucoma [56].

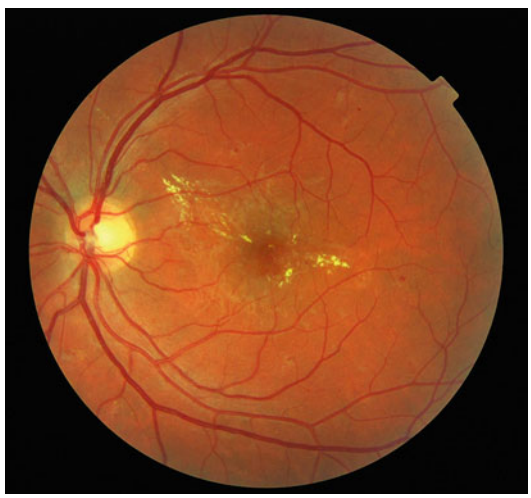

Fig. 9 Showing microaneurysms, *dot* haemorrhages. The sheen over the macula is due to attached vitreous usually seen in young patients (Reproduced, with kind permission, from Dr. P. Nithianandan)

Treatment

Treatment of DR is crucial even though there is no cure. With early diagnosis and treatment the more likely vision loss will be prevented or delayed. It is also related to the blood pressure and glycaemic control, and there is ample evidence that the effects of diabetes on the retina can be delayed or even curtailed by rigorous control of the blood sugar level [58], blood pressure and possibly lipids [53]. Tight control of the blood sugar and the blood pressure is strongly advocated. Systemic agents especially hypoglycaemic, hypolidaemic and antihypertensive have been shown to reduce the progression of DR [59]. The beneficial effects of two types of drugs (fenofibrate and candesartan) on diabetic retinopathy have been publicised [60, 61]. Fenofibrate is used to treat hypertriglyceridaemia and mixed dyslipidaemia [62], and the long-term use of fenofibrate could reduce the need for laser treatment in a large number of cohorts of type 2 diabetic patients [62]. It had been shown to reduce the frequency of laser treatment for DME and PDR [62]. Renin-angiotensin system (RAS) in the eye plays an important role in the pathogenesis of DR and RAS blockade that can promote higher beneficial effects in DR compared to other antihypertensives [62, 63].

The efficacy of laser treatment (photocoagulation) in PDR and in significant DME has been demonstrated [64], although it has not been uniformly favourable in preventing visual decline [62]. In patients with persistent DME and DR, intravitreal corticosteroid therapy has shown clinical benefits and shown best corrected visual acuity (BCVA) [59]. Compared with laser or placebo, studies assessing steroids have produced mixed results [65]. Direct intravitreal injections have been associated with risks of elevated intraocular pressure and cataract [59, 66]. Attention now had been directed towards the development of novel intravitreal delivery devices [59] such as

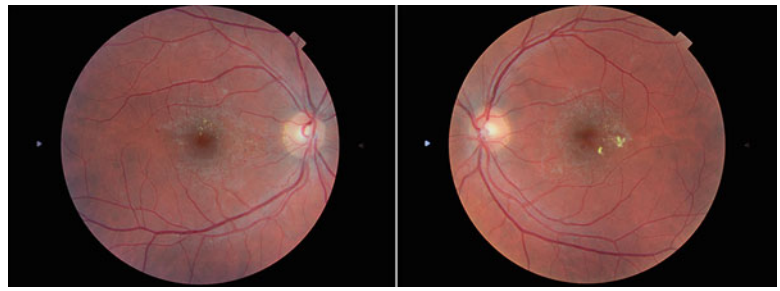

Fig. 10 Shows exudative maculopathy, hard exudates encroaching in the area of the macula (Reproduced, with kind permission, from Dr. P. Nithianandan)

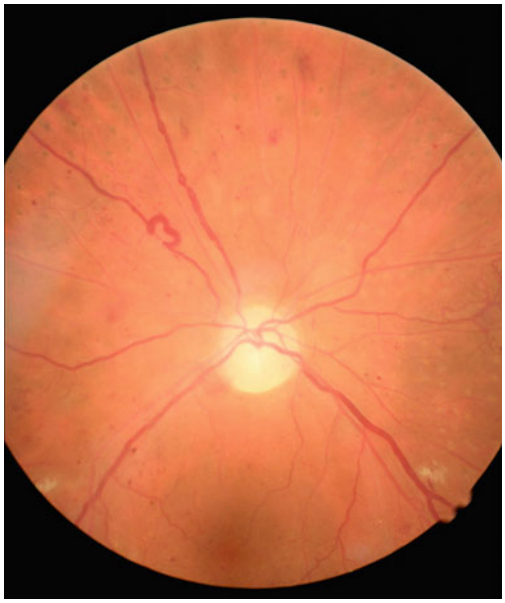

Fig. 11 Shows venous abnormalities including dilated veins, venous looping, venous beading, blotchy haemorrhages and cotton-wool spots (Reproduced, with kind permission, from Dr. P. Nithianandan)

intraocular implants which provide prolonged and controlled drug release thus averting side effects associated with repeated intravitreal injections [67].

Antiangiogenic agents (anti-vascular endothelial growth factor) have been found to be effective in the treatment of DR and DME [59]. Local administration of anti-VEGF via intravitreal injections would avoid systemic side effects such as hypertension, proteinuria and impaired wound healing [62]. However, repeated injections may increase local complications such as vitreous haemorrhage, retinal detachment and traumatic cataract [62]. At present four anti-VEGF drugs are available: ranibizumab, bevacizumab, pegaptanib sodium and aflibercept. In patients with PDR, intravitreal bevacizumab and ranibizumab are gaining acceptance as a clinical adjunct to photocoagulation [59]. Surgical removal of the vitreous (vitrectomy) is done in case of vitreous haemorrhage or retinal detachment (Box 4).

Impact of Low Vision in the Elderly

Low or loss of vision can have negative consequences for patients. It greatly affects the health and well-being and changes their ability to perform everyday activities and their ability to drive, causing problems with walking and increasing the risk of falls [68]. The common causes of vision loss are age-related macular degeneration, glaucoma, cataract and diabetic retinopathy [1, 2]. In the elderly, AMD is the leading cause of irreversible blindness and low vision [69] and causes permanent loss of vision than glaucoma and diabetic retinopathy combined [70]. Health-related quality of life refers to patients' perspective of their health status relating to functioning and well-being [71]. The health-related quality of life of people with visual impairment is generally greater than those living in the community at large. The impact of low vision or loss on functioning and quality of life is compromised in terms of functional restrictions and activity limitations. Visual impairment threatens the independence of the elderly and has large economic and social costs. There have been a number of studies on the impact of glaucoma on patients. Glaucoma is associated with a decrease in the quality of life [35]. Bilateral glaucoma is associated with cessation and limitation of driving, slower walking and falls [72]. In a study of 165 patients aged

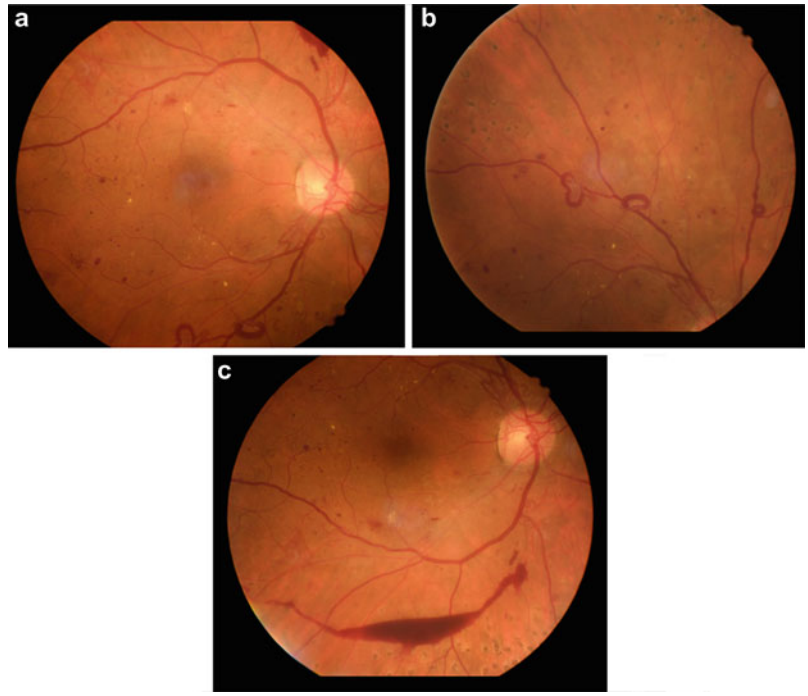

Fig. 12 (**a**) New vessels at the disc (NVD) and new vessels elsewhere (NVE) observed in the infratemporal retina and below inferior temporal vessels. (**b**) New vessels elsewhere (NVE) in the region of the venous loops and cotton-wool spots. (**c**) Shows NVE in the inferior temporal better of vitreous haemorrhages (preretinal haemorrhage) between the retina and the vitreous hence the fluid level. Figure (**b**) and (**c**) shows panretinal laser photocoagulation scars at the periphery of the retina avoiding the macula area (Reproduced, with kind permission, from Dr. P. Nithianandan)

70–79 years with glaucoma of varying severity, mild, moderate and severe, it was found that depression was more prevalent with increasing glaucoma severity [73]. In another study assessing the impact of DR on quality of life, the participants had vision-related activity limitations, socio-economic issues, frustrations due to visual restrictions and restrictions with driving, social life and in relationships [74]. DR is a leading cause of blindness in the working age group worldwide [75].

Multiple Choice Questions

1. A 75-year-old man has age-related macular degeneration. Each of the following statements are true, EXCEPT:
   A. AMD is responsible for 48% of severe vision loss in Australia.
   B. Those with a family history of immediate family members with AMD are at higher risk.
   C. Men are more at risk than women.
   D. Smokers are three times at risk of developing AMD.
2. A 72-year-old woman is seen with age-related macular degeneration. Each of the following symptoms and signs are true, EXCEPT:
   A. Vision may be distorted and there is loss in discriminating colours.
   B. Peripheral vision is affected more than central vision.
   C. The soft drusen are larger and tend to confluent and specific for AMD.
   D. The wet (exudative) type is characterised by the development of choroidal neovascularisation.
3. The following management options for age-related macular degeneration (AMD) are true, EXCEPT
   A. Lutein and zeaxanthin are found in green vegetables – spinach, broccoli and Brussels sprouts among others.
   B. Lifestyle changes can play a role in reducing the risk of developing AMD.
   C. Specific high-dose antioxidants significantly reduce the risk of advanced AMD.
   D. Even if AMD reaches the advanced-stage treatment can prevent vision loss.

4. The following statements are true of glaucoma, EXCEPT:
   A. Open-angle glaucoma is the most common and usually affects both eyes.
   B. Risk factors include age, family history, diabetes, hypertension and injury.
   C. In the subgroup – normal tension glaucoma even though the intraocular pressure remains normal – visual field loss occurs due to nerve damage.
   D. Central vision is the first to be affected.
5. The following management options for glaucoma are true EXCEPT:
   A. There is a cure for glaucoma.
   B. Currently there is a shift in the first-line treatment from beta-blockers to prostaglandins derivatives.
   C. Acute angle-closed glaucoma is a medical emergency.
   D. Usually topical drug therapy is used first.
6. The following statements on cataract are true EXCEPT:
   A. Age-related cataracts usually affect both eyes.
   B. Usually presents with blurred vision and pain.
   C. Day glare and headlights at night while driving as the cataract progresses.
   D. It occurs in diabetes, with smoking and alcohol and those taking medications like corticosteroids.

MCQ Answers

1 = C; 2 = B; 3 = D; 4 = D; 5 = A; 6 = B

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Blurred Vision

85

Contents

Abstract

Blurred vision is a very common eye complaint. The patient's perception of blurred vision may vary. It is important to clarify from the patient what exactly he or she means by blurred vision. This chapter briefly summarises the differential diagnosis of blurred vision.

Keywords

Blurred vision · Unilateral · Bilateral · Pain

Introduction

The patient's perception of blurred vision may vary from objects seen indistinctly, distortion of images, double vision, changes in the distinctness of the images, reduced field of vision and interference with the images such as due to flashes of light or floaters. Blurred vision is a very common eye complaint. It is important to clarify from the patient what exactly he or she means by blurred vision. It is important to determine and divide whether the blurring of vision affects one or both eyes, its mode of onset, sudden or gradual, whether associated with pain or not. This is useful but is arbitrary for example acute angle closure glaucoma could affect both eyes but usually one eye (Fig. 1).

Unilateral sudden and painful

Anterior uveitis usually presents with pain, photophobia, red eye and decreased vision with perilimbal flush and pupillary miosis.

Traumatic hyphema requires urgent referral to ophthalmologist.

It may be followed glaucoma and recurrent bleeding.

Acute angle closure glaucoma presents with headache, eye pain, halos, dilated pupils, red eye, decreased vision, nausea and vomiting. It is a medical emergency [35].

Temporal arteritis is diagnosed because of an episode of anterior ischaemic optic neuropathy.

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_93

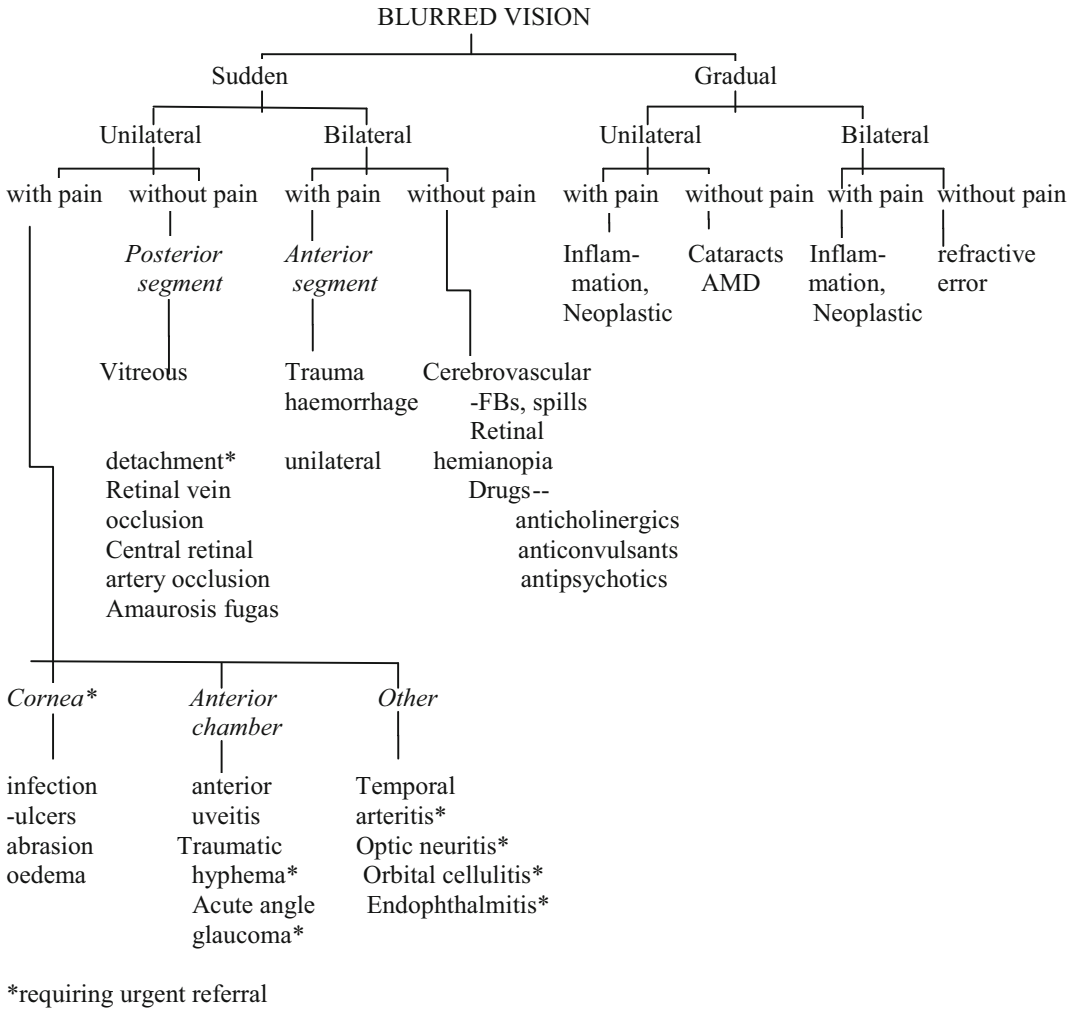

Fig. 1 Shows the differential diagnosis of blurred vision (Information sources: Best Practice [1] Medical diagnosis [2]; patient.co.uk [3]; patient.co. [4])

Optic neuritis may affect one or both eyes with transient decreased vision and usually associated with multiple sclerosis.

Orbital cellulitis usually follows paranasal sinusitis and is characterized by orbital pain, oedema of the eyelid and redness, decreased movements of the eye and exophthlamos together with fever.

Endophthalmitis caused by intraocular infection presents with severe pain and decreased vision.

Unilateral sudden without pain

Vitreous haemorrhage is extravasation of blood into the vitreous and result from retinal vein occlusion, retinal tears, diabetic retinopathy, trauma and retinal neovascularization. Retinal detachment could follow.

Retinal detachment is painless and early symptoms include flashes of light or blurred vision. The patient often notices a veil or curtain in the field of vision.

Retinal vein occlusion characterized by engorged retinal veins and multiple haemorrhages on fundus examination. It occurs usually in the elderly and presents with painless visual loss.

Central retinal artery occlusion occurs suddenly with loss of vision in affected eye. Ophthalmoscopy reveals a pale opaque fundus with a red fovea.

Amaurosis fugas or transient monocular blindness (TMB) involves one eye with reduced vision which is transient lasting for a sew minutes. It is the equivalent of transient ischaemic attack (TIA). It an indicator of carotid artery involvement and is limited to stroke – aged population.

Evaluation of Impaired Vision in the Elderly

A clear patient history in respect of onset, duration, course, pattern of visual impairment, association with pain and the presence of other diseases must be recorded. Acute onset is suggestive of retinal detachment or a vascular event. Because of changes in the vitreous humour retinal detachment is common in the elderly. Severe eye pain, reducing vision, headache, nausea and vomiting is suggestive of acute closed angle glaucoma. Gradual and progressive visual loss points to conditions such as cataract, age-associated macular degeneration or glaucoma.

Examination of the eyes in the elderly should be a routine practice in geriatric care. It has to be remembered that there no single test specific or definite for screening but the use of combination of methods may assist in arriving at a diagnosis. Visual inspection may reveal lens opacities. Visual acuity is tested by the standard Snellen eye chart, each eye tested separately and if the letters cannot be read the pinhole test helps to distinguish changes in vision from refractive from a more serious disease. If the vision improves with pinhole the problem is more likely to be refractive. Reading is tested with Jaeger's. The intraocular pressure is measured by tonometry. In normal adults the mean intraocular pressure is 15–16 mmHg and the normal range is 10–20 mmHg.

Impact

Blurred vision causes significant impairment of functional status and quality of life [5]. Blurred vision caused greater limitations on physical health problems compared to that of hypertension, diabetes mellitus, history of myocardial infarction amongst others [5]. Cognitive assessment revealed that performance on non-verbal tests was significantly affected in patients with blurred vision but verbal test performance was not affected [6] (Box 1).

Box 1 Key Points. Blurred Vision

It is important to clarify from the patient what exactly he or she means by blurred vision.

It is important to determine and divide whether the blurring of vision affects one or both eyes, its mode of onset, sudden or gradual, whether associated with pain or not.

It is important to clarify from the patient what exactly he or she means by blurred vision.

It is important to determine and divide whether the blurring of vision affects one or both eyes, its mode of onset, sudden or gradual, whether associated with pain or not.

Acute onset is suggestive of retinal detachment or a vascular event.

Extended Matching Questions

A. Temporal arteritis
B. Acute angle glaucoma
C. Endoophthalmitis
D. Orbital cellulitis
E. Anterior uveitis
F. Papilloedema
G. Optic neuritis

The following patients have in common blurring of vision. Choose the most likely diagnosis from the list above. Each option can be used only once.

1. Patient presented with headache, eye pain, halo, dilated pupils, red eye, decreased vision with nausea and vomiting.
2. History of parasinusitis and characterized by orbital pain, oedema of the eyelids and redness, decreased movements of the eye and exoptththlmos together with fever.
3. Patient complains of transient visual blurring, occurring as he rose from bed or chair (obscuration).
4. Patient presented with photophobia, red eye and decrease vision with perilimbal flush and pupillary miosis.
5. Complains of temporal headache with scalp tenderness and sudden painless deterioration of vision in one eye.
6. Patient with multiple sclerosis experiences transient decreased vision in both eyes occurring usually after exercise.

EMQ Answers

1 = B; 2 = C; 3 = F; 4 = E; 5 = A; 6 = G

Case Study: 78-Year old with Blurred Vision A 78-year old male presented with blurred vision in the left eye. He has had bilateral lens extractions with posterior chamber implants. The first was done 2 years earlier without any complication and the second about a week prior to his development of the visual problem. He had no co-morbid illnesses like diabetes or hypertension. He was seen by the Ophthalmic Surgeon. Angiography revealed fluorescein leakage into the macula and together with the clinical history was consistent with a cystoid macular oedema (Irvine Gass syndrome). He was prescribed Maxidex (Dexamethasone) eye drops two hourly and Voltaren (diclofenac sodium) eye drops six hourly. When seen at the end of 2 weeks his vision was back to normal.

Comment: Cystoid Macular Edema (CME) follows disruption of the permeability barrier of the retina resulting in accumulation of fluid in the outer plexiform layer of the of the central macula and classified as angiographic or as clinically significant. It is a common complication following unreventful cataract surgery but can result from a variety of conditions such as diabetes, uveitis, central retinal vein occlusion amongst others. First described by Irvine after cataract surgery [7] and subsequently the angiographic description by Gass and Norton [8] and hence known as Irvine-Gass syndrome. The symptoms are blurred or decreased vision and this depends on the extent of the oedema. Fluorescein angiography is the gold standard which shows typical petaloid appearance of the fluorescein leakage. This is largely being replaced with optical coherence tomography (OCT). There are several treatment options and corticosteroids remain the mainstay of treatment and include topical, periocular and intravireal injections. Non-steroidal anti-inflammatory drugs (NSAIDS) are equally effective [9]. Acetzolamide, bevaciziemab and anti-VEGF are other options [9].

Information sources: Irvine [7], Gass and Norton [8], and Warren [9]

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Dry Eye

86

Contents

Abstract

Dry eye syndrome (DES) is caused by alterations to the tear film and anterior surface of the eye. It is a common problem. Patients with DES complain of itchiness, stinging or burning or a feeling of a foreign body in the eye and tired eye. If untreated, it may lead to damage of the cornea, transient fluctuations of vision and blepharitis.

Keywords

Dry eye · Sjogren's · Blepharitis · Tarsorrhaphy

Introduction

Dry eye embraces a group of conditions characterised symptomatically by irritation, gritty and burning eyes and caused by alterations to the tear film and anterior surface of the eye [1]. It is a common problem. It is estimated that 33 million Americans have some form of dry eye syndrome [1]. The lacrimal gland located in the upper eyelid produces the aqueous layer, and several other smaller glands (meibomian) in the lids produce the mucous and lipid layers. In the corner of the eye near the nose are two ducts which drain the excess tears into the nasal passage. The tear film is the fluid that covers the cornea and the conjunctiva and protects the cornea from drying, increases its refractory power and protects it against irritation [2]. It is made up of three layers [1], the mucous layer, the middle aqueous layer and the outer lipid layer. It is the lipid or oily layer that seals the tear film on the eye and protects the cornea by preventing evaporation.

Dry eye syndrome (DES) may occur as the result of (i) decreased tear production, (ii) excessive tear evaporation and (iii) abnormality in the production of mucous and lipid layers. Decreased tear production (i) and excessive tear evaporation (ii) give rise to decrease in the aqueous layer, and decreased production may be the result of medications and hormonal changes as in menopause or related to

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_94

autoimmune disorders. Decrease in the lipid layer production occurs with ageing [1].

Causes

The cause is multifactorial. Age is an important factor [3] as tear production decreases with advancing years. Women at the onset of menopause complain of dry eyes. The other factors include hot, dry climates, air-conditioning, prolonged contact lens use, irritants such as smoking or chemical exposure, some medications (oral contraceptive pills, antihistamines, diuretics and antidepressants) and vitamin A deficiency, and diseases such as Sjogren's, rheumatoid arthritis, lupus and Parkinson's disease can cause dryness [4, 5].

Symptoms

Patients with DES complain of itchiness, stinging or burning or a feeling of a foreign body in the eye and tired eye. Sometimes there may be excessive tearing occurring intermittently. Irritation of the eye due to dryness initiates a reflex giving rise to increased production of tears.

Treatment

If untreated, it may lead to damage of the cornea; there may be transient fluctuations of vision, and one may suffer from inflammation of the eyelids (blepharitis) manifesting as itching sensation, with crusting of the eyelashes and/or eyelids. Sitting in front of the computer for long periods of time should be avoided. It is essential to make an effort to blink frequently and to maintain adequate hydration. Eye drops, commonly referred to as artificial tears, may be used. Eye lubricants, cyclosporine, corticosteroid drops, non-steroidal anti-inflammatory drugs (NSAIDs) and eye drops are used according to the needs of the patient. Antibiotic drops and oral preparations should be taken when indicated. In some instances, surgery is required in the form of inserting punctual plugs and tarsorrhaphy where there is difficulty in closing the eyes.

Impact

Several studies to evaluate the impact of dry eye syndrome (DES) on vision-related quality of life have revealed significant impairment of quality of life (QoL) [6, 7] including aspects of physical, social and psychological functioning [8]. It has also been shown that moderate to severe dry eye caused decrease in QoL akin to that in severe angina, dialysis and disabling hip fractures [8, 9].The use of hydroxypropyl cellulose ophthalmic inserts reduced signs and symptoms of moderate to severe DES and improved QoL and activities of daily living [10] (Box 1).

Box 1 Key Points. Dry Eye

It is due to decreased tear production, excessive tear evaporation or abnormality of mucous and lipid layers [1].

If untreated, it may damage the cornea.

One may suffer from inflammation of the eyelids (blepharitis), infections and decreased QoL [5].

Eye lubricants, cyclosporine, corticosteroid drops, non-steroidal anti-inflammatory drugs (NSAIDs) and eye drops are used according to the needs of the patient.

Multiple Choice Questions

1. The following are true of dry eye syndrome, *except*:
   A. Dry eye syndrome (DES) may occur as the result of decreased tear production.
   B. Dry eye syndrome (DES) may occur as the result of decreased tear evaporation.
   C. If untreated, it may lead to damage of the cornea.

D. Women at the onset of menopause complain of dry eyes.

MCQ Answers

1 = B

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Part XX

Skin Disorders in the Elderly

With aging structural and functional changes occur in all the structures of the skin. With normal aging process a number of extrinsic factors act to prematurely age the skin. Chronic sun exposure over the years causes changes to the skin. Skin diseases in the elderly are more often than not the effects of sun damage or vascular disease. In both community dwelling elderly and nursing home residents, seborrheic keratosis and xerosis have the highest prevalence exceeding over 75%, but in the dermatologic clinic, the presenting conditions are actinic keratosis, fungal infections, and xerosis. Pruritic eruptions are common in the elderly especially in those in their 70s and 80s. Melanoma is the fourth common cancer and is due to an uncontrolled growth of the pigmented cells, the melanocytes. The susceptibility of the elderly to infectious diseases, autoimmunity, and cancer is directly or indirectly related to age-related changes of the immune system. Immunosenescence leads to occurrence of autoimmune skin disorders such as bullous pemphigoid, paraneoplastic pemphigus, and pemphigus vulgaris and in older women lichen sclerosus and potential reactivation of the zoster virus. Psoriasis is a complex disease characterized by a chronic autoimmune-mediated inflammation. Population studies have shown the prevalence of leg ulcers in the aged 65 years and older to be between 0.12% and 3–5%, and the prevalence increases with age to over 5% in those aged 80 years and over. Part XX summarizes the common skin conditions in the elderly, their prevalence, mechanisms, and clinical management.

Common Skin Disorders in the Elderly 87

Contents

Abstract

Skin diseases in the elderly are more often than not the effects of sun damage or vascular disease. In both community-dwelling elderly and nursing-home residents, seborrheic keratosis and xerosis have the highest prevalence exceeding over 75%, but in the dermatologic clinic, the presenting conditions are actinic keratosis, fungal infections and xerosis. Pruritic eruptions are common in the elderly especially those in their 70s and 80s. Melanoma is the fourth common cancer and is due to an uncontrolled growth of the pigmented cells, the melanocytes. Immunosenescence leads to occurrence of autoimmune skin disorders such as bullous pemphigoid, paraneoplastic pemphigus and pemphigus vulgaris and in older women lichen sclerosus and potential reactivation of the zoster virus. Psoriasis is a complex disease characterised by a chronic autoimmune-mediated inflammation. This review summarises the common skin conditions in the elderly, their prevalence, mechanisms and clinical management.

Keywords

Photoageing · Actinic keratosis · Fungal infections · Xerosis · Pruritic eruptions · Melanoma

Introduction

The epidermis consists of four types of cells. The keratinocytes (90%) produce protein keratin, and it protects the skin and inner tissues. The melanocytes (8%) contribute to the colour of the skin and absorb ultraviolet light and transfer granules of

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_89

melanin into the keratinocytes. The third type of cell is the Langerhans cell, and their role is to interact with helper T cells in immune responses. The Merkel cell is in the deepest layer of the epidermis and believed to function with the sensation of touch. The dermis is composed of elastic fibres and collagen, and the deeper layer known as the reticular region provides the skin with elasticity, extensibility and strength. In the subcutaneous layer, there are nerve endings called Pacinian corpuscles.

The most common skin conditions affecting the elderly are eczematous dermatitis [1, 2], pruritus [1, 3, 4] and fungal and viral infection [1, 3]. In a study of community-dwelling elderly and nursing-home residents, seborrhoeic keratosis and xerosis had the highest prevalence, and other conditions seen were actinic keratosis and fungal (tinea unguium) infections [5]. Onychomycosis (tinea unguium) was frequently seen in the elderly, in males more than in females [6, 7]. The elderly showed a threefold increase in pruritus compared to younger patients 60 years and less attending the outpatients [3]. In older women lichen sclerosus was common involving the genital area [2]. The common cutaneous tumours in the elderly are basal cell carcinoma, actinic keratosis, Bowen's disease and squamous cell carcinoma [3]. The susceptibility of the elderly to infectious diseases, autoimmunity and cancer is directly or indirectly related to age-related changes of the immune system [8].

Clinical Manifestations

Benign Conditions

Seborrhoeic keratosis is usually seen in patients over the age of 50, and most Caucasians are affected sooner or later [9]. It manifests as verrucous plaques and has a warty 'stuck on' appearance and a greasy feeling to touch. There is a localised hypertrophy of the basal layer in the epidermis. The areas involved are generally those exposed to sunlight such as the face, neck and trunk. Vitamin D3 supplements have been reported to improve the lesions [9].

In the elderly the common dermatoses seen are xerosis, pruritus, eczematous dermatitis and stasis dermatitis [2]. Seborrhoeic dermatitis is significantly more prevalent in the elderly [2] and is characterised by red itchy skin with flaky scales and looks like psoriasis. It is more common in men and occurs on the face especially around the nose, behind the ears, navel, below the breasts and groins. Treatment includes shampoos containing zinc pyrithione, selenium sulphide or ketoconazole [10] for the scalp. Xerosis cutis (xeroderma) is characterised by a dry itchy skin, with fine or white flaky scales and fine cracks in the skin involving more especially the arms and legs. Two formulations light (oil in water) and rich (water in oil) containing glyceryl glucoside, natural moisturising factors and ceramide have been shown to be beneficial in the treatment of xerosis [11]. Stasis dermatitis affects about 7% of older adults who are generally obese and manifests as swelling of the feet followed by dermatitis – scaly red oedematous plaque [10]. The elderly who are ageing and who are malnourished are prone to develop asteatotic eczema which usually involves the lower extremities (Fig. 1).

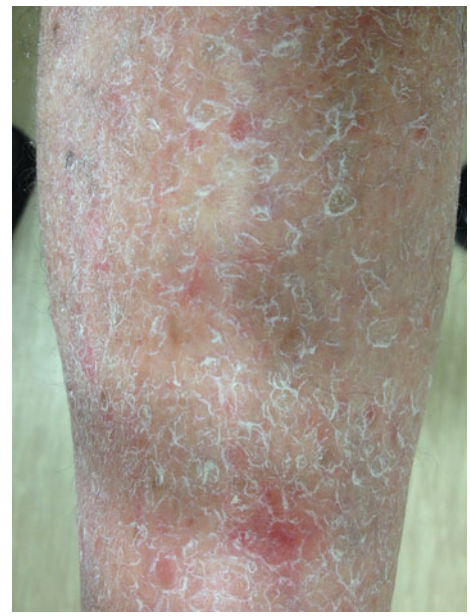

Fig. 1 Asteatotic eczema shows cracked skin likened to "crazy pavement pattern" (Reproduced, with kind permission, from Dr. Derek Davies, Orange Dermatology)

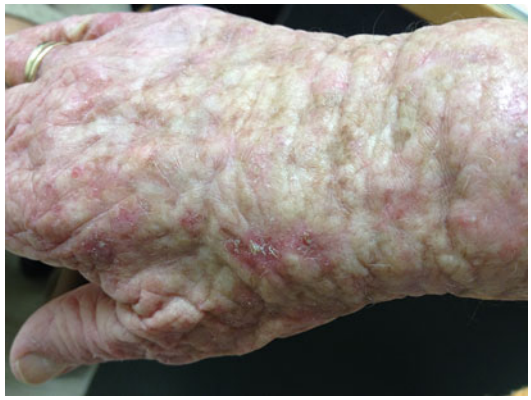

Fig. 2 Actinic keratosis – rough, red scaly papules, easily palpated than seen (Reproduced, with kind permission, from Dr. Derek Davies, Orange Dermatology)

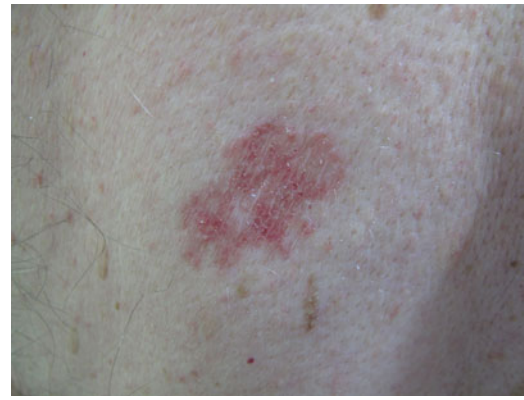

Fig. 3 Bowen's disease shows red scaly plaque with well-defined margins (Reproduced, with kind permission, from Dr. Derek Davies, Orange Dermatology)

Premalignant Conditions

Actinic keratosis is usually seen after the age of 65 and results from continued exposure to solar radiation. They are common after the age of 45 years in the Caucasian Australians [12]. Many of the lesions regress but a few, estimated at about 5–20% [10, 13], may progress to squamous cell carcinoma within 10–25 years [14]. The lesions appear as rough, red scaly papules and are easily palpated than seen [15] (Fig. 2). They are more often seen over sun-exposed areas, the head, the forearm and the back of the hands [10], and most often removed by cryotherapy (liquid nitrogen) [16] or curettage and topical application of 5-fluorouracil [10]. Lentigo appears as a slowly enlarging macule with irregular borders. It is an in situ melanoma of chronically sun-damaged skin. It has to be distinguished from solar lentigines which are smaller with regular borders and homogenous in colour and are benign growths [10].

Bowen's disease is squamous cell carcinoma in situ and is characterised by red scaly plaque with well-defined margins most often in the lower limbs [16] (Fig. 3). It is a disease of the elderly and the mean age at diagnosis is in the sixth decade [17]. It can occur anywhere on the skin or mucous membranes. There is a 3–5% risk of developing invasive squamous carcinoma [18]. Internal malignancies are often associated with multiple lesions and need close follow-up.

Malignant Skin Disorders

Basal cell carcinoma is a common malignant skin condition [3]. It has been reported that 50% of Caucasian Australians will develop basal cell carcinoma before the age of 70 years [12] which is most common in older adults. Exposure to the sun is the major risk factor [19]. Typical lesions are firm and have a pearly appearance and telangiectasia on its surface and rolled borders. Other signs include a nodule varying in colour red, pink or white and translucent or an area resembling a scar (Fig. 4). They enlarge slowly [16] and are usually found on the sun-exposed areas of the head and neck in fair-skinned individuals. Some appear as a scaly plaque with raised pearly edge. They rarely metastasise [12]. Treatment options are curettage and cautery or excision and radiation [15], and there is a high risk of recurrences requiring long-term monitoring [20].

Squamous cell carcinoma is another common tumour of the skin occurring in about 13.3% of the elderly above the age of 65 years [3]. It usually occurs in the same fair-skinned individuals as basal cell cancer in the chronically sun-exposed areas but occasionally in sites of previous ulceration like chronic venous ulcers or other skin damage like radiodermatitis. It is the most common type of skin cancer in dark-skinned people. The early lesions are red papules or plaques, and the overlying epidermis may be scaly or hyperkeratotic with irregular borders,

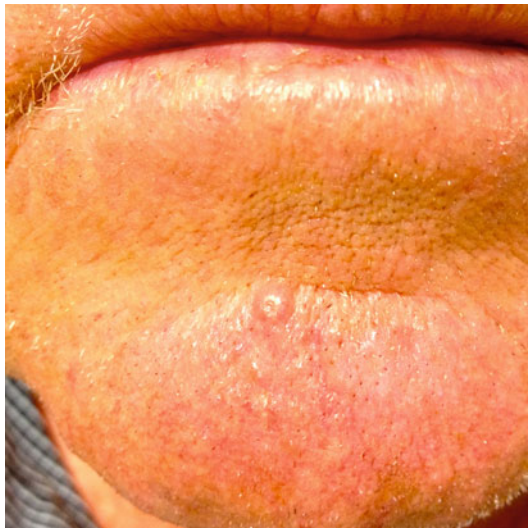

Fig. 4 Basal cell carcinoma shows a solitary shiny nodule on the chin (Reproduced, with kind permission, from Dr. Derek Davies, Orange Dermatology)

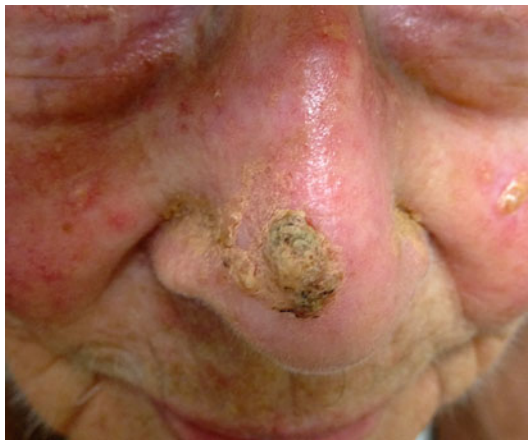

Fig. 5 Squamous cell carcinoma shows scaly elevated hyperkeratotic and irregular borders. The surrounding skin shows signs of sun damage (Reproduced, with kind permission, from Dr. Derek Davies, Orange Dermatology)

rapidly increasing in size, and the more advanced ulcerates and bleeds easily when touched (Fig. 5).

People at risk of developing melanomas are shown in Box 1.

1. The common subtypes of melanoma are (i) lentigo maligna (Hutchinson's freckles) (Fig. 6), (ii) lentigo maligna melanoma (Fig. 7), (iii) nodular melanoma and (iv) superficial spreading melanoma. Lentigo maligna is a pre-malignant macular lesion with an irregular border and variegate pigmentation [15], and treatment options are surgical excision, laser surgery and cryotherapy [15].

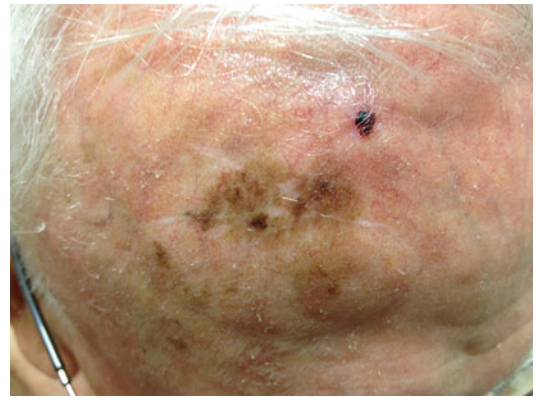

Fig. 6 Lentigo maligna (Hutchinson's freckles) (Reproduced, with kind permission, from Dr. Derek Davies, Orange Dermatology)

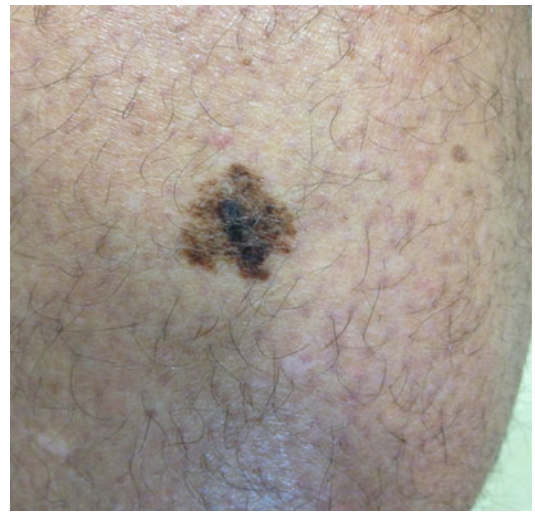

Fig. 7 Lentigo maligna melanoma characterised by irregular border and varied coloration (Reproduced, with kind permission, from Dr. Derek Davies, Orange Dermatology)

In a study of 610 patients with malignant melanoma, 237 patients were above the age of 75 years, and it had been shown that malignant melanoma was more common in men, and the clinical and pathological expression were different to that of

their younger counterparts [22]. The investigators found the elderly patients presented with thicker melanomas, and this was attributed to delayed diagnosis and a higher mitotic rate but with fewer sentinel lymph node metastases [22]. There is greater incidence of head and neck involvement that sets down to cumulative photo damage [22] and starts in the pigment cells and melanocytes of the skin. The lesions are brown or black in colour and usually asymmetrical. Melanoma is an aggressive and highly metastatic cancer [23]. During the past decade, melanoma has been considered to be a spectrum of melanocytic malignancies characterised by mutations in several kinases such as BRAF, NRAS and KIT [24]. BRAF mutations are present in two thirds of cutaneous melanomas [23, 25]. About 40–60% of patients have activating BRAF mutation in their melanotic cancer [26]. The most common mutation is V600E followed by V600K [27]. The remaining has NRAS mutations [25], and they tend to have thicker tumours and a higher mitotic rate [28]. Tumours that do not have BRAS or NRAS are referred to as wild type for BRAF and NRAS [28]. These mutations occur in the mitogen-activated protein kinase (MAPK) pathway [25] and are a common site for genetic deviations in melanoma.

Box 1 Causative Factors in Melanoma

Fair skin
Family history
UV radiation
With unusual moles – dysplastic nevi
Depressed immune system
Had previous melanoma

Information source: Cancer Council Australia [21]

Diagnosis

The ABCDE system is used to ascertain whether a lesion is a melanoma or not.

(A) Asymmetry: Melanomas are usually asymmetrical.
(B) Border: The borders are usually irregular in melanomas.
(C) Colour: Within the dark blue-black background of the melanoma, there is a colour variation – red, white, grey or violet.
(D) Diameter: The diameter is usually 6–7 mm when first diagnosed.
(E) Elevation: Raised lesions have a poor prognosis.

Diagnosis Is by Skin Biopsy

The American Joint Committee on Cancer (AJCC) carried out major revisions of the melanoma TNM and stage grouping criteria [29]. The staging criteria involved both the tumour-node-metastasis (TMN) criteria and stage grouping for all four stages of melanoma [29]. Major changes include:

1. Melanoma thickness and ulceration but not level of invasion to be used in the T-cell category [29, 30].
2. The number of metastatic lymph nodes rather than their gross dimensions to be used in the N classification [29, 30].
3. The site of distant metastases and the presence of elevated serum lactic dehydrogenase (LDH) to be used in the M classification [29, 30].
4. All patients with stage I, II or III disease will be upstaged when the primary melanoma ulcerates.
5. Merging of satellite metastases around the primary melanoma, an in-transit metastasis grouped into stage III disease.
6. Distinct definitions for clinical and pathologic staging gained from intraoperative lymphatic mapping and sentinel node biopsy [29, 30].

Prognosis

There are a number of features which affect the prognosis, more importantly the tumour thickness (Breslow's depth) and depth related to structures (Clark level). Breslow describes the thickness of the tumour in millimetres and in four categories, and Clark level describes how deeply it has penetrated (number 5) [31]. Important prognostic information is based on histological examination [32, 33]. Other prognostic features are shown in Box 2. If the tumour is detected before it has spread, 99% will be alive in 5 years, but if it has spread, the

5-year survival will be 65% and if widespread 15%. Age is an independent poor prognostic factor [22], and overall survival was worse in those over the age of 50 years [34] (Box 2).

Box 2 Prognostic Features in Melanoma

Location of lesion
Presence of satellite lesions
Type of melanoma
Presence of ulceration
Presence of lymphatic involvement
Presence of regional or distal metastasis
Presence of tumour infiltrating lymphocytes

Information source: Homsi et al. [35], Dickson and Gershenwald [36]

Treatment

Prevention is by avoidance of sunburn.

For thin melanoma, surgery is curative and requires that the melanoma and 1–2 cm of normal skin around are removed. If drainage lymph nodes are involved, they should be removed. For thick melanomas some centres offer high-dose interferon after surgery and, for widespread disease chemotherapy, drugs such as dacarbazine and biologicals such as interferon or interleukin-211. Increase in our knowledge of molecular biology and immunology has led to the recognition of therapeutic targets and the development of new systemic agents which have revolutionised the treatment of metastatic and unresectable melanoma [37–39]. The molecular targets include (i) the MAP kinase signals such as BRAF mutation and (ii) mitogen-activated protein kinase (MEK) [37, 38]. Melanoma has high immunogenicity and cytokines [38] and has led to (i) immunomodulation targeting the ligand CTLA-4 (cytokine T lymphocyte-associated antigen) and (ii) those targeting T-cell ligands such as programmed cell death protein-1 (PD1)-PD1 ligand (PDL1) [38, 39]. A number of drugs (dacarbazine, interleukin-2 (IL-2), vemurafenib, ipilimumab, dabrafenib and trametinib) have been approved and are being used for adjuvant therapy and to treat metastatic disease [40]. Dacarbazine and IL-2 have been used for metastatic disease. Vemurafenib and dabrafenib are inhibitors of mutated BRAF, and trametinib a MEK inhibitor has been shown to have excellent efficacy in clinical studies [38]. The BRAF inhibitors in combination with MEK inhibitors have been shown to have great potential [39]. CTLA-a antibody (ipilimumab) has improved overall survival, and those targeting T-cell ligand and the anti-PD1/PDL1 antibodies (pembrolizumab, nivolumab) [37] have shown a higher response rate than ipilimumab [38].

Autoimmune Skin Disorders

The immune response is affected by the decrease in the Langerhans cells with ageing [41]. Immunosenescence leads to similar levels of occurrence of autoimmune skin disorders such as bullous pemphigoid, paraneoplastic pemphigus and pemphigus vulgaris and in older women lichen sclerosus and potential reactivation of the zoster virus [2]. These autoimmune skin disorders result from either the production of antibodies that react with the host tissue or to autoreactivity of the immune effector T cells [42]. Autoimmunity to hemidesmosomal proteins present in the base membrane of stratified squamous epithelia results in bullous pemphigoid, and paraneoplastic pemphigus results from autoimmunity to multiple desmosomal antigens [43]. Dermatomyositis is an autoimmune systemic disorder [42] which manifests with cutaneous eruptions and inflammatory myopathy [42, 44]. In the elderly dermatomyositis is associated with underlying malignancies and commonly associated with malignancies from the colon, breast, lung and uterus [44]. Lichens sclerosus has an increased risk of squamous cell carcinoma in the elderly [42].

Bullous pemphigoid is an acute or chronic autoimmune disease and is seen in the elderly over the age of 70 years. It is a subepidermal blistering disease, and the generalised form is the most common presentation. It has a predilection for the arms and legs, and occasionally the oral or ocular mucosa may be involved. The blisters usually last for a few days and then heal without

leaving a scar. Diagnosis is confirmed by biopsy or immunofluorescence studies [15]. Treatment is with oral prednisone and at times azathioprine as a steroid-sparing drug [15].

Psoriasis

Psoriasis is a complex disease characterised by a chronic autoimmune-mediated inflammation [45]. The incidence has been estimated at 60.4 per 100,000 person years in one cohort study [46]. The dermis and epidermis are colonised by T lymphocytes triggering an inflammation with an increase in the proliferation of keratinocytes and resulting in red raised and scaly plaque-like lesions (Fig. 8) with a wide range of phenotype manifestations [45]. Two distinct subtypes (type I and type II) of psoriasis have been recognised which differ in the age of onset [47] and in the frequency of HLA [48]. In type I (or early onset) which has onset before the age of 40 years [45], the frequency of HLA, Cw6, B57 and DR7 is strongly increased [48], whereas in type II (or late onset) which has onset after the age of 40 years with a peak age between 57 and 60 years [49, 50] has HLA-CW2 over-represented [48]. HLA-Cw6 is present in 85.6% of patients with early onset and only 14.7% in the late onset [49]. The early onset displays a strong family history and is strongly associated with HLA allele specifically HLA-C*-06 [45] with extensive and severe skin involvement [47] and increased incidence of guttate and eruptive type of psoriasis, nail involvement and higher incidence of Koebner's phenomenon [47, 51] The early onset has a greater tendency to become generalised and has an irregular course [49]. The late onset follows a less severe course with palmoplantar pustulosis [47]. It is associated with increased cardiovascular comorbidities [52–54] and a higher prevalence of metabolic syndrome [54]. Table 1 shows some of the similarities and differences between early-onset and late-onset psoriasis. Depression and anxiety are seen in elderly women with psoriasis, and its influence on the quality of life (QoL) is high [55].

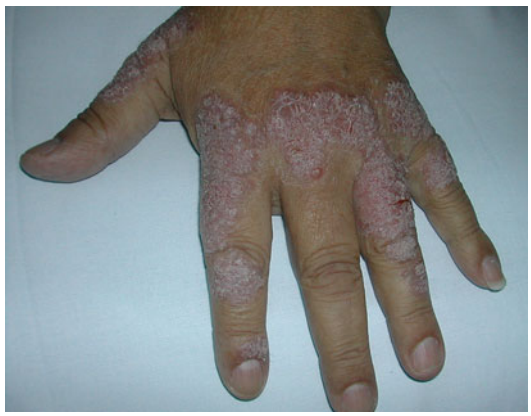

Fig. 8 Shows red raised and scaly plaque-like lesions in psoriasis (Reproduced, with kind permission, from Professor Nicholas Manolios)

Viral Infections

Herpes zoster is caused by reactivation of the varicella-zoster virus [6, 56]. Acyclovir was the

Table 1 Shows the differences and similarities between early-onset and late-onset psoriasis

Age of onset	Early onset <40 years) (peak onset 16–22)	Late onset (>40 years) (peak onset 57–60)
Genetics		
HLA-Cw6	~85%	~15%
Heritability	Strong family history	Sporadic
Clinical manifestations	Severe, extensive skin	Less severe
	Guttate, nail involvement	Palmoplantar pustulosis
Comorbidities		
Cardiovascular risk		Increased risk
Metabolic syndrome		Increased risk
Psychiatric disorders	Common	Common
Psychosocial impact	Greatly impaired	Less impaired

Information sources: Queiro et al. [45], Henseler and Christpher [49], Fernandiz et al. [47], Gudionsson et al. [51], Fernandez-Torres et al. [52], and Armesto et al. [53]

standard treatment over the years. Presently the newer antivirals famciclovir and valacyclovir offer less dosing [6]. HHV-6, HHV-7 and HHV-8 are three recently discovered human herpes viruses which may cause a primary infection, establish a latent infection and then reactivate when conditions of altered immunity develop [56]. HHV-6 and HHV-7 have been linked with roseola (especially HHV-6) and severe drug reactions (especially HHV-6) and pityriasis rosea (mostly HHV-7). The alpha-herpesviruses (HSV types 1 and 2 and varicella-zoster virus) cause blistering skin diseases. The gamma-herpesviruses (Epstein-Barr, HHV-8) induce cellular proliferation and malignancy [57]. In the elderly herpes simplex virus (HSV) commonly affects the vermilion border of the lip, and of great concern is that recurrent herpes labialis has the potential to autoinoculate the eye and genitals [56]. Prophylaxis of herpesvirus infection in the elderly involves the prevention of HSV and complications of herpes zoster [58].

Fungal Infections

In the elderly the more frequently found fungal infection is onychomycosis and presents as subungual infection affecting usually the big toe and as white superficial onychomycosis involving the third or fourth toes [7, 59]. It is caused most commonly by trichophyton rubrum and T mentagrophytes [59]. In recent years it has increased in prevalence and attributed to increased longevity and comorbid conditions such as diabetes [60]. Candida onychomycosis affects fingernails more often and is accompanied by paronychia [60].

Parasitic Infestations of the Skin

The more common epidermal parasitic skin diseases are scabies caused by *Sarcoptes scabiei* and pediculosis caused by lice. Scabies and pediculosis capitis and pediculosis pubis occur worldwide, but pediculosis corporis is confined to the cold climate [61].

Scabies

The scabies mite (*Sarcoptes scabiei*) is a tiny ectoparasite that infests human beings. It burrows under the skin. Transmission is by direct skin-skin contact, and incubation period is between 4 and 6 weeks.

The clinical presentation is typical in normal scabies (scabies vulgaris) with raised burrows or slightly raised red nodules on the back of the hands, wrists and in between the fingers. It may also be found in the genitals and in women the breasts. Itching is severe especially at night. Secondary infection can occur in the long-standing cases with pustular formation which may persist even after successful treatment. In immunocompromised, mentally retarded and elderly patients, the clinical presentation may be altered [62]. The clinical features in the elderly differ from those in the younger individuals, and such episodes are often the cause of nosocomial outbreaks. This is largely because of the delay in diagnosis due to non-specificity of the lesions [63] and is especially the case of the elderly diagnosed with psychiatric or degenerative disorders.

In crusted (scabies norvegica) scabies, continued scratching destroys the burrows resulting in crusts. It may have a more general distribution involving the axillary areas, trunk, head and neck. In the elderly scratching may not occur due to the physical inactivity or inability to scratch or lack of itching. Several cutaneous, immunological and neurological disorders are known to predispose to crusted scabies [64]. Diagnosis is from the history of itching and the identification of the mites or their faeces from skin scrapings. The diagnosis can be difficult especially in the elderly.

Treatment

Topical scabicides include malathion (Quellida-M; Derbac-M) and permethrin (Lyclear Dermal Cream) as first-line treatments, the former in the case of adults 100 ml for 24 h, two applications 1 week apart, and the latter one to two tubes 8–12 h [65]. Oral ivermectin is given in a single dose of 200 umg/kg orally in the treatment of crusted scabies, in outbreaks and in immunocompromised patients at the discretion of the consultant dermatologist [65]. Treatment is applied to

the whole body paying attention to the webs of fingers and toes. It is important that all members of the staff and residents be treated simultaneously. Clothing and bed linen should be machine-washed. Residents with scabies need not be isolated, but those with crusted scabies require isolation [65].

Pediculosis

Pediculosis due to the human body lice is caused by *Pediculus humanus humanus* also called *Pediculus humanus corporis*. Pruritus in a homeless person or a person living in an institution in which the clothing and bedding are not changed regularly should raise the possibility of lice as a cause. Pruritus is the initial symptom of pediculosis and is the result of an allergic reaction to the louse saliva. There is generalised excoriation and pyoderma may be present. It lays eggs in clothing rather than at the base of hairs. The body louse may be confined in the seams of clothing. Body louse is a serious threat to possible contagion of diseases such as typhus. Treatment is by boiling all clothes and bed linen and daily bathing and wearing clean clothes. Oral ivermectin at a dose of 12 mg on 0, 7 and 14 days had been used in a small trial [66]. Head louse is caused by *Pediculus humanus capitis* and is spread by direct head-to-head contact, and characteristic symptom is pruritus in the head.

Impact

Skin disorders have a high impact on the elderly, and these include pruritus, ulceration, bacterial infections and fungal disease, among others. Pruritus has a significant impact on the quality of life and sleep in elderly patients [67]. The painful and itchy symptoms affect the social life and their personal relationships [68]. It affects the lives of partners and family members in many aspects of everyday life [68]. They are stigmatised and often frowned upon and avoided for fear of infection [68]. Psychiatric disorders are common in patients with skin disorder [69]. Major depressive symptoms are common [32], and a study revealed that 32% of patients with psoriasis have depressive symptoms [70]. There is a high prevalence of suicidal tendency among patients with psoriasis [71]. The All-Party Parliamentary Group on Skin in the United Kingdom drew attention to the severe impact of skin diseases which affected all aspects of people's lives with obvious sense of desperation, frustration and often isolation [72] (Box 3).

Box 3 Key Points. Common Skin Disorders in the Elderly

The most common skin conditions affecting the in the elderly are eczematous dermatitis [1, 2] pruritis [1, 3, 4], fungal and viral infection [1, 3].

The common cutaneous tumours in the elderly are basal cell carcinoma, actinic keratosis, Bowen's disease and squamous cell carcinoma [3].

Melanocytic malignancies are characterized by mutations in several kinases such as BRAF, NRAS and KIT [24].

The common clinicopathological subtypes of melanoma are (i) lentigo maligna (Hutchinson's freckles), (ii) lentigo maligna melanoma (iii) nodular melanoma and (iv) superficial spreading melanoma.

Skin diseases in the elderly are more often than not due to the effects of sun damage or vascular disease.

The immune response is affected by the decrease in the Langerhans cells with aging [41].

Immunosenescence leads to similar levels of occurrence of autoimmune skin disorders such as bullous phempigoid, paraneoplastic pemphigus and pemphigus vulgaris [2].

Multiple Choice Questions

1. The following are true relating to age-related changes in the skin, EXCEPT:
   A. About 80% of facial ageing is due to sun exposure.
   B. There is an increased number of melanosome synthesised resulting in increased pigmentation.

C. There is a reduction of immune cells in the skin compromising immune response.
D. There is impaired circulation to the skin with ageing.

2. The following are true of primary dermatological disorders, EXCEPT:
   A. Actinic keratosis is usually seen after the age of 65 years.
   B. Most Caucasians are affected sooner or later by seborrhoeic keratosis.
   C. Basal cell carcinoma metastasises early.
   D. In Bowen's disease there is 3–5% risk of developing invasive squamous carcinoma.
3. The following are true of melanomas, EXCEPT:
   A. Melanomas are usually symmetrical and have regular borders.
   B. Important prognostic information is based on histological examination.
   C. If the melanoma had widely spread, the 5-year survival is about 15%.
   D. Australia has the highest incidence of melanoma and represents 10% of all cancers.

MCQ Answers

1=B; 2=C; 3=A; 4=A

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Pruritus in the Elderly

88

Contents

Abstract

Pruritic eruptions are common in the elderly especially in those in their 70s and 80s. Broadly, pruritus can be due to a primary dermatological disorder or to an underlying system disease. A wide variety of systemic diseases is associated with pruritus, and in 10–50%, it is an important intimation of an underlying system disease.

Keywords

Pruritus · Pruritic eruptions · Itch · Pruritogens · Parasitosis

Introduction

Itching or pruritus is a desire to scratch and is often considered to be synonymous though the term pruritus is generally taken as itching without any apparent diagnostic skin lesions. It is common among the elderly over the age of 65, and its incidence increases with advancing age.

Classification

Based on the pathophysiology, pruritus has been categorised into four types [1, 2]: (i) pruritoceptive initiated in the skin by inflammatory or pathological process, e.g. scabies and urticaria; (ii) neurogenic generated in the central nervous system, a response to circulating pruritogens as in cholestasis; (iii) neuropathic due to anatomical lesions of the central or peripheral nervous systems, for example, nerve entrapment; and (iv) psychogenic including delusional parasitosis [3, 4].

Causes of Pruritus in the Elderly

Pruritic eruptions are common in the elderly especially in those in their 70s and 80s [5]. Broadly, pruritus can be due to a primary dermatological disorder or to an underlying system disease. The most common dermatosis in the elderly are the eczemas. Other primary rashes include urticarial,

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_88

psoriasis, scabies, lichen planus, pemphigus, dermatitis herpetiformis and cutaneous lymphoma [6]. Eczemas are inflammatory skin conditions characterised by pruritus, erythema oozing, crusting and scaling. It may be brought about by a number of factors such as irritants and allergic sensitisation, and in a number of instances the cause is not known. It presents with pruritus, excoriation of the skin and lichenified areas, but these are frequently only secondary lesions and may be mistaken for primary dermatitis [7].

There are several types of eczema. Atopic eczema and contact dermatitis are not so common in the elderly though they are seen. Seborrhoeic dermatitis, stasis dermatitis (gravitational eczema) and discoid (nummular) eczema are common. Seborrhoeic dermatitis usually affects the face, scalp and body flexures.

Bullous pemphigoid is a blistering disorder affecting the elderly, and it usually occurs after the age of 60. Men and women are affected equally. An autoantibody is produced to the basal layer of the epidermis. The skin develops erythematous lesions with pruritus often in intertriginous areas. The blistering can be extensive. The mucous membranes of the conjunctivae and mouth may be involved. Occasionally, certain drugs such as frusemide, captopril or penicillin may be associated at the onset. Confirmation is by skin biopsy and immunofluorescent staining which shows C3 deposits of the complement in all patients and IgG along the dermal-epidermal junction.

Common skin infestations are scabies, pediculosis and tinea. Scabies mite is an ectoparasite, and its presentation is characteristic except in the mentally retarded, immune-compromised and elderly patients. This group of patients often reside in institutions.

A wide variety of systemic diseases is associated with pruritus, and in 10–50%, it is an important intimation of an underlying system disease [8] (Box 1). In patients with pruritus due to xerosis which is persistent and refractory to treatment, a search for systemic cause should be made. Chronic renal failure is a well-known cause of generalised pruritus. Itching may occur in severe paroxysms in uraemia especially in warm weather. Pruritus occurs in about 25% of patients with chronic renal disease and in about 86% on haemodialysis [9]. It is unclear at what degree of renal failure pruritus occurs. Generalised pruritus is associated with the haematological malignancies and may occur several years before the disease manifests. In one-third of the patients with Hodgkin disease, intense, generalised pruritus is the presenting symptom in cutaneous T-cell lymphoma [10].

Box 1 Systemic Causes of Pruritus

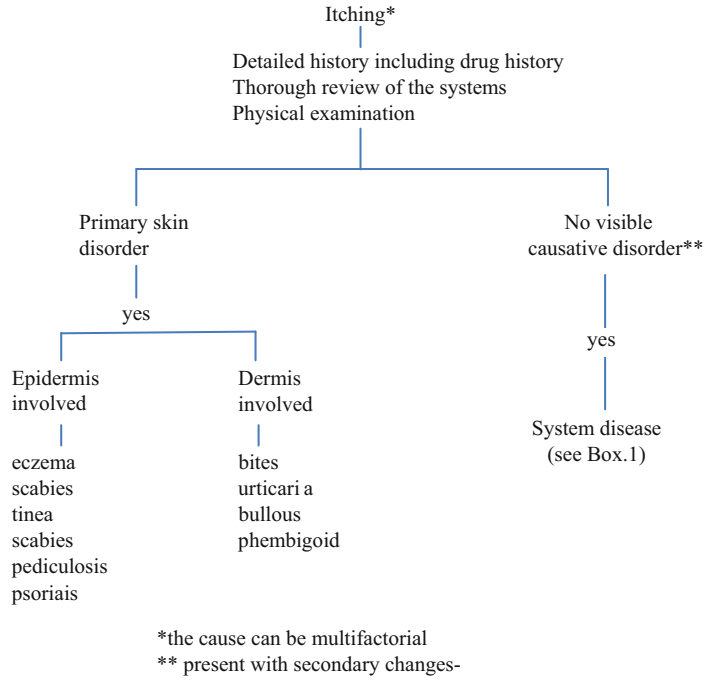
Chronic renal failure	Extra-hepatic obstruction
Polycythaemia rubra vera	Hepatitis
Hodgkin disease	Drug ingestion
Non-Hodgkin lymphoma	Opiate ingestion, leukaemias
Visceral malignancies	
Multiple myeloma	Psychosis
Iron deficiency anaemia	Stroke, space-occupying lesions
Hyperthyroidism/ hypothyroidism	Diabetes mellitus
Malignant carcinoid	

Information sources: Bernhard [6], Ward and Bernhard [7]

Along with uraemia, cholestasis is responsible for the most severe itching [11]. Cholestasis-related pruritus occurs usually at night and has a predilection for the hands and feet [11]. Cholestasis may also be caused by drugs such as oral contraceptive pills, phenothiazines, erythromycin and anabolic steroids. Other drugs which could induce pruritus are the opiates and its derivatives, aspirin, quinidine and vitamin B complex [6].

Delusional parasitosis is a belief that the skin is infested with insects, worms or organisms. It could be produced by a variety of organic processes: toxic, metabolic and structural disorders. It may occur as a monosymptomatic delusional belief or be one of a number of manifestations of paranoid psychosis [12]. Delusion parasitosis and organic delusional disorders share a common topography of brain lesions involving the subcortical and limbic brain areas in either hemispheres [13] and with lesions from various sites [14].

Algorithm 1 Evaluation of Pruritus.



Algorithm 1 shows a step-by-step evaluation of a patient with pruritus.

Treatment

If untreated, it may lead to scratch-related complications such as bacterial infections and lichen planus chronicus. There have been several reports of gabapentin, serotonin antagonists, cutaneous field stimulation and ultraviolet B therapy of some benefit in some patients [7].

Impact

It is important to recognise and treat these patients, as severe pruritus is very distressing with increased irritability, affecting sleep and quality of life [11]. Chronic pruritus is a significant threat to overall QoL [15, 16]. It has an impact equivalent to chronic pain [17]. It can lead to impaired sleep and cause depressive symptoms and anxiety [16]. In haemodialysis patients, pruritus affects morbidity and increases mortality, and this has been attributed to poor sleep that it causes [18] (Box 2).

Box 2 Key Points: Pruritus

Pruritus is common among the elderly over the age of 65 and its incidence increases with advancing age [5].

Broadly, pruritus can be due to a primary dermatological disorder or to an underlying system disease.

A wide variety of systemic diseases is associated with pruritus, and in 10–50%, it is an important intimation of an underlying system disease [8].

Chronic renal failure [9], haematological malignancies, Hodgkin disease, cutaneous T-cell lymphoma, cholestasis [10] and delusional parasitosis are known to cause generalised pruritus [12].

Multiple Choice Questions

1. The following are true of pruritus in the elderly except:
   A. Itching can occur with severe paroxysms in uraemia in the cold weather.
   B. In one-third of patients with Hodgkin disease, generalised pruritus is the presenting symptom.

C. Delusional parasitosis can be a manifestation of paranoid psychosis.
D. Generalised pruritus is associated with haematological malignancies and may occur several years before the disease manifest.

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Chronic Leg and Foot Ulcers in the Elderly

89

Contents

Abstract

Chronic leg ulcer can be defined as an ulcer that has not healed after 3 months of appropriate treatment. Peak prevalence is between 60 and 80 years. Arterial ulcers are the second largest group of leg ulcers and account for 10–25% of lower limb ulcers. Venous ulcers are the most common in those 65 years and older. Diabetes patients can develop both arterial and neuropathic ulcers. Pressure ulcers range from 7% to 23% among nursing home residents. Chronic ulcers of the skin affect several aspects of daily life and changes in functional capacity. This chapter will provide an overview of leg and foot ulcers, prevalence, clinical manifestations and management.

Keywords

Chronic leg ulcer · Arterial ulcers · Venous ulcers · Neuropathic ulcers · Pressure ulcers

Introduction

Leg ulcers are defined as a breakdown or discontinuity of the skin and subcutaneous tissues and may extend to involve the muscle and bone [1] of more than 6 weeks in duration [2]. Chronic leg

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_87

ulcer can be defined as an ulcer that has not healed after 3 months of appropriate treatment [3]. Population studies have shown the prevalence of leg ulcers in the aged 65 years and older to be between 0.12% [4] and 3–5% [5], and the prevalence increases with age to over 5% in those aged 80 years and over [6]. Peak prevalence is between 60 and 80 years [7]. About 2% of the ulcers are unrelated to arterial or venous disease [8], and vasculitis, malignancy, metabolic abnormalities and infection are unusual causes [8, 9]. Koerber found 75.5% venous ulcers, 3.65% arterial, 14.66% mixed and 13.5% vasculitic ulcers among 354 leg ulcers [10]. Vasculitic ulcers are usually associated with rheumatoid arthritis and polyarteritis nodosa [11].

Clinical Manifestations

Ischaemic Ulcers

Arterial ulcers are the second largest group of leg ulcers [11] and account for 10–25% of lower limb ulcers [1]. Factors that worsen leg and foot ulcers include smoking, hypertension, diabetes, advanced age, coronary artery disease and arthritis. Nicotine has a peripheral vasoconstrictive action and increases the risk of ulceration. Arterial ulcers are usually below the ankle especially on the toes [11]; the base is yellow, brown or black in colour or necrotic base [12], dry with margins punched out and sharply demarcated [13].

Venous Ulcers

Venous ulcers are the most common in those 65 years and older [14]. The prevalence of venous ulcers varies from 0.1% to 1% [15–17] and accounts for almost 80% of all leg ulcers [18, 19]. Venous insufficiency or occlusion or both are complications of deep vein thrombosis, and the long-term problems arising from them are venous ulcers [20]. Venous ulcers are usually located between the ankle and calf, between the malleoli and often on the medial aspect of the leg [6]. Factors which aggravate venous ulcers include congestive heart failure, obesity, diabetes, fracture or injury and physical inactivity. Venous ulcers have an irregular border, shaggy shape and ruddy granulating base [12] with moderate to heavy exudate [13].

Neuropathic Ulcers

In neuropathy the motor, sensory and autonomic fibres are involved. Diabetes patients can develop both arterial and neuropathic ulcers for they are at higher risk of developing arterial disease and neuropathy [6]. The lifetime risk of developing foot ulcers is as high as 25% in a diabetic [21], and the major underlying causes are ischaemia from peripheral arterial disease and peripheral neuropathy [6]. Good glycaemic control delays or slows the progression of the neuropathy [22]. In a cross-sectional survey, peripheral vascular disease was present in 67% of all ulcerated legs in patients with diabetes, and ulcer solely attributed to possible neuropathy was 15% [23]. The common locations are both feet at increased pressure points. The base of the neuropathic ulcers is variable, the margins are punched out [13], and there is a rim of hyperkeratotic tissue.

Pressure Ulcers

In 2004, 11% of about 159,000 nursing home residents in the USA had pressure ulcers [24]. The prevalence of pressure ulcers ranges from 9.2% in acute hospitals [25] at the time of admission to 17.4% [26] −35% [27] in nursing homes. The presence of high-grade ulcers amounts to 4% in the elderly in nursing care facilities [28]. Pressure ulcers range from 7% to 23% among nursing home residents [27]. In general practice, the prevalence of pressure ulcer in the 65 years of age and older varied from 0.31% to 0.70% and is most likely to occur in those over 85 years of age [14]. The common sites are the sacrum, ischium, trochanter, ankles and heels. Their appearance and margins are dependent on the stage of the ulcer.

Evaluation

An accurate diagnosis is essential for proper management of leg ulcers. The common types of ulcers can be made by a careful history, physical examination and non-invasive testing [29]. Complete assessment should include the patient's health as well as specific findings of the skin, vascular status [9], limb and ulcer [30]. An examination of the ulcer should include the location, size, appearance, ulcer base, exudates and surrounding skin [30].

Diabetics should be tested for developing neuropathy. One way of detecting sensory loss in the physician's surgery is the use of the nylon monofilament. The monofilament is pressed against the foot with just enough pressure to bend the filament at the test sites [31]. There is a risk of ulcer formation if the patient is unable to feel the monofilament. A vascular assessment includes duplex ultrasound, ankle-brachial index, haemocoagulation status and photoplethysmography [17]. X-rays should be done when there is a suspicion of bone involvement and films to be inspected for signs of osteomyelitis which include periosteal reaction, cortical erosion and osteopenia [1]. The normal range of ankle-brachial pressure index (ABPI) is 0.5–1.2. An ABPI of less than 0.5 and more than 1.2 requires vascular assessment [11]. In diabetics, medial calcification of the tibial vessels may falsely elevate the ankle pressure [1]. ABPI should be recommended as a screening test. MRI and bone scan are useful in establishing the diagnosis of bone infection [1].

Management

Preventive Measures

The commonest causes are vascular insufficiency and diabetes. A very large number of diabetic foot complications resulting in amputation begin with the formation of a skin ulcer. Regular screening for neuropathy, podiatric care and custom footwear may reduce the risk of foot ulcers [22]. Early detection and appropriate treatment may prevent amputation in the vast majority of patients. A number of studies have shown that primary care physicians perform foot examinations infrequently [32, 33]. General practitioners are in ideal situations to ensure that all patients and especially those at risk receive early and optimum care for skin ulcers. Correcting the underlying cause rather than the ulcer is the key to successful prevention and treatment of leg ulcer. Patient's role should daily inspect for breaks in the skin and in the foot, areas of rubbing and signs of infection with proper management of minor injuries [34]. There should be strict attention to foot care, cleaning with soap and water [34]. Topical moisturisers should be used to prevent cracks and drying. The use of harsh topical agents, hot soaks and heat pads should be avoided. It is advisable not to walk barefoot and to wear well-fitting shoes [34].

Ill-fitting footwear or any chronic disease such as rheumatoid arthritis and diabetes may give rise to foot deformities. Some of the more common foot deformities are hammer or claw toes, callus, bunions [35] and a lowered medial longitudinal arch. Foot pressures and possibly shear stress may result from foot deformities contributing to the development of ulcers. Factors contributing to foot pressures include joint deformities, callus, limited joint mobility, bony prominences, neuropathic joints, previous foot surgery, inappropriate footwear, walking barefoot, falls and accidents.

Treatment depends on the underlying cause and factors that have prevented healing and should be addressed.

Venous Ulcers

The main aim is to reduce oedema and venous hypertension by adequate compression [15], and elevation of the legs may improve cutaneous microcirculation [36]. Compression is the mainstay of treatment [17, 37, 38] preceded by debridement [17]. In the elderly, double bandages (zinc paste and elastic compression) are used and changed once weekly [36]; however, multilayer bandaging appears to be cost-effective [9]. When pain is present, a modified compression is

recommended [11]. Simple adherent dressings may be used to control exudates, aid healing and enhance comfort in venous ulcers. Infection should be treated, and appropriate pain relief should be prescribed. Systemic therapy with pentoxifylline or aspirin [16] or flavonoids may help to counteract the inflammation [38]. Pentoxifylline has been reported to improve venous ulcer healing with or without compression therapy [39]. Other supplements to compression therapy are autologous grafts, growth factor therapy [16, 40] and venous surgery [16] such as the use of radiofrequency for ablation of superficial truncal veins or sclerotherapy [35]. Treatment may involve wound cleansing, application of dressings and anti-inflammatory treatment. After healing compression therapy should be continued with stockings with a level of 30–40 mmHg. Patients with venous insufficiency and peripheral obstructive arterial disease may benefit by gait training. A malignancy may present in a lower leg ulcer, and if suspected especially if the ulcer is not healing, a punch biopsy should be performed. The relative risk of malignancy in chronic venous ulcers is 5.8% [17].

Neuropathic Ulcers

The management of neuropathic ulcer once it has developed is by pressure relief, debridement and treatment of infection. Debridement allows good granulation and epithelialisation.

Arterial Ulcers

Re-establishment of adequate blood supply often through is the cornerstone in the management of arterial ulcers.

Pressure Ulcers

Debridement is the first step, and this can be surgical, osmotic, autolytic and chemical enzymatic. The treatment should include adequate nutrition including protein, zinc and vitamin supplements as indicated.

Impact

The elderly have an increased susceptibility to skin disorders, and this largely related to age-related changes, ongoing extrinsic damage and environmental insults [1]. Chronic ulcers of the skin affect several aspects of daily life, changes in functional capacity [41], pain, impaired mobility and sleep and emotional stress resulting in social isolation [42–44]. Herber et al. [45] evaluated the impairment of QoL in patients with chronic leg ulcers and found they had higher levels of pain, function and emotional limitations compared to controls. Venous ulcer pain has been descried as aching, stabbing, sharp and tiring and overall affected the health-related quality of life [46]. Pain is a significant feature and caused restrictions in people's lives [47]. Leg ulceration has a high incidence of recurrence [48]. There is a feeling of disgust, self-loathing and low self-esteem in patients with chronic leg ulcers [49] (Box 1).

Box 1 Key Points. Leg Ulcers

Chronic leg ulcer can be defined as an ulcer that has not healed after 3 months of appropriate treatment [3].

Arterial ulcers are the second largest group of leg ulcers [11].

Arterial ulcers are usually below the ankle especially on the toes [11].

Venous ulcers are the most common in those aged 65 years and older [14].

Venous ulcers are usually located between the ankle and calf, between the malleoli and often on the medial aspect of the leg [6].

Diabetic patients can develop both arterial and neuropathic ulcers for they are at higher risk of developing arterial disease and neuropathy [6].

(*continued*)

Box 1 Key Points. Leg Ulcers (continued)

The common locations are both feet at increased pressure points. The common sites of pressure ulcers are the sacrum, ischium, trochanter, ankles and heels.

ABPI should be recommended as a screening test. An ABPI of less than 0.5 and more than 1.2 requires vascular assessment [11]. The main aim in venous ulcers is to reduce oedema and venous hypertension by adequate compression [15].

Multiple Choice Questions

1. A 72-year-old woman with diabetes presented with numbness and tingling of her extremities for the past 6 months and an ulcer on her right foot. She was on an oral hypoglycaemic agent. On examination of the lower limbs, there were diminished sweating, dryness and fissuring of the skin of both feet together with deformities. The peripheral pulses were felt and were equal. There was reduced sensation – she was unable to feel with microfilament. The reflexes were reduced with loss of position sense.

   Which additional finding would suggest a diagnosis of a neuropathic rather than an ischaemic ulcer?

   A. The ulcer was located on the ball of the right big toe.
   B. The base was yellow brown and blackened in areas.
   C. The skin surrounding the ulcer is red when foot is dangling and pale when elevated.
   D. It was painful at night.

2. A 75-year-old man noted pain in his right thigh and calf on walking about 100 m over the past 8 weeks making him to stop walking. He becomes free of pain in 3–4 min after he had stopped walking. He also said of an ulcer on his right foot which was painful especially at night and not healing. He was obese, hypertensive and diabetic and had been smoking about 30 cigarettes for 40 years. On examination there were skin and nail changes and an ulcer on the tips of the second and third toes of his right foot. The pulses were normal in the inguinal region. Pulses could not be felt distally.

   Which additional finding would suggest a diagnosis of an ischaemic ulcer rather than a neuropathic ulcer?

   A. Foot – red when dangling but pale when elevated.
   B. Sensation was reduced.
   C. Ulcers on pressure points.
   D. Reflexes diminished.

MCQ Answers

1 = A; 2 = A

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Part XXI

Oral and Oral-Related Disorders in the Elderly

Oral health is an essential component to an elderly's general health and quality of life. Part XXI provides an overview of the prevalence and mechanisms followed by management and prevention of dental caries, periodontal disease, edentulism, and tooth wear. Oral health declines with age leading to high levels of tooth loss, dental caries, and the prevalence rates of periodontal disease, ill-fitting denture, mucosal lesions, oral ulceration, xerostomia, and oral pre-cancer and cancer. Oral health is one of the most influential factors in ill health, involving ill health in a vicious cycle and terminating in impaired QoL. The review includes related disorders such as bruxism, temporomandibular dysfunction, myofascial pain, and osteonecrosis of the jaw. Many systemic diseases have oral manifestations and they must be recognized. The primary care physician and the dental professional must be familiar with these for appropriate treatment and management of older patients with these conditions.

Oral Issues in the Elderly

90

Contents

Abstract

Oral health is an essential component to an elderly's general health and affecting quality of life. Oral health declines with age leading to high levels of tooth loss, dental caries and the prevalence rates of periodontal disease, ill-fitting denture, mucosal lesions, oral ulceration, xerostomia and oral precancer and cancer and has been evident in older people with poor oral health globally. Caries, attrition and abrasion increase with age. Periodontitis has worldwide prevalence and affects individuals of all ages but is most common in the elderly. The proportion of pathological tooth wear in the 65 years and older people is three times that seen in people aged 26–30 years. Edentulism increases with age and in the 75 years and older with 31.5% being females and 9.6% males. This chapter provides an overview of the oral issues in the elderly, their prevalence and clinical care.

Keywords

Oral health · Caries · Periodontitis · Tooth wear · Edentulism

Introduction

The elderly have been categorised as young old between the ages of 65 and 74 years and between 75 and 84 years and oldest old those above 85 years. Current demographic findings predict an increase in the elderly population worldwide. The oldest old (>over 85 years) group is said to be a rapidly growing segment of the population [1]. In Australia 3.1 million people were over the age of 65 years in 2011 [2]. In the United States, the size of the projected older population will double over the next 30 years to 70 million by 2030 [3], and projections of population aged 85 and older could grow from 4 million in 2000

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_92

to 19 million by 2050 according to the US Census Bureau [1]. A proper understanding of the changes related to ageing and their significance is necessary to develop appropriate corrective/remedial strategies. Although ageing is normally associated with age-related changes, most of these changes do not cause oral diseases [4, 5].

Basic health services are an indispensable part of primary health care. Oral health is an essential component to an elderly's general health and affecting quality of life [6, 7] and is often neglected in the elderly [8, 9]. Oral health declines with age [9] leading to high levels of tooth loss, dental caries and the prevalence rates of periodontal disease [9], ill-fitting denture, mucosal lesions, oral ulceration, xerostomia and oral precancer and cancer [10] and has been evident in older people with poor oral health globally [11]. Chewing, eating habits and nutritional intake can compromise oral health. Poor oral health can contribute to malnutrition, systemic diseases, speech deficits and facial deformity. Furthermore, systemic diseases or their treatment can lead to risk of oral disease. Periodontitis may heighten the susceptibility to systemic disease [12]. Oral organisms have been the source of infection of the meninges, endocardium, mediastinum, vertebrae, prosthetic joints and hepato-biliary system [13]. In the United States, 12% of the population over the age of 60 years consume 30% of all prescription medicine, many of them can have a negative impact on oral health [14, 15]. Most of the elderly have more than one chronic condition [1], and the ageing patient's health state is complicated by systemic diseases [3]. The frequently occurring conditions are hypertension, diabetes mellitus, cardiovascular diseases, arthritis and cancer [1]. Other conditions that are common to the elderly are cognitive, sensory and physical impairments [15]. The elderly exhibit a range of cognitive impairments from mild cognitive impairment to frank dementia [16]. All these problems may increase in magnitude with advancing age.

In Australia most elderly live with family members in private dwellings, and the living arrangements vary by age, gender and degree of dependence for activities of daily living [2]. According to the Australian Bureau of Statistics, more women than men lived alone; 69% of women and 38% of men were widowed [2]. Most elderly prefer to stay at home as long as possible depending on their health status, availability of caregivers [3] and the need for assistance with long-term care. In Australia in 2011, the 2% of people aged 65–74 years increased to 6% aged 75–84 years and 26% aged 85 years and over and lived in non-private dwellings (nursing homes and accommodation for the retired or aged) [2].

Berkey et al. [17] in a review of oral health studies of institutionalised elderly between 1970 and 1989 described the compromised oral health status of nursing home residents. Up to 70% of the residents exhibited dental caries, edentulism, periodontal disease, poor oral hygiene and soft tissue lesions. In a global overview of oral health conditions in older people (71% of WHO member states), it was documented that dental caries and periodontal diseases were a considerable public health problem in the majority of the countries and the prevalence of tooth loss varied according to the region and national income [18].

The older adult requires special attention in relation to oral health care. They differ in patterns of disease and prevalence rate and have features which may affect the management and the method by which they are performed, and furthermore the elderly often have problems such as impaired mobility in accessing the health-care delivery system [19]. Countries must adopt positive strategies for improving the oral health of the elderly as recommended by the World Health Organization [11].

Clinical Manifestations

Caries

Caries, attrition and abrasion increase with age [20]. Root caries is the most significant dental problem among older adults [21], and more than half of the individuals 75 years and older have caries [22]. Coronal or root caries are the main cause of tooth loss in more than half of the older patients who are dentate [23]. In the United States, the Third National Health and Nutrition Examination Survey between 1988 and 1994 revealed that one

third of the adults 65 years of age and older had untreated dental cavities, more so in older black persons and poor persons [24]. There is evidence that in the elderly, the exposed root surfaces in combination with compromised health status and multiple medications increase the risk of root caries [14]. Coronal and root caries are a significant problem especially in those who are dependent, cognitively impaired and medically compromised [25]. Another study found the high levels of oral disease in nursing home residents were due to the poor health status and the great impact of dementia [26].

There are two types of caries based on the location, coronal and root caries. The coronal caries are recorded as (i) non-cavitated and (ii) cavitated. The root caries are also of two types. (i) Early carious root lesions involve the small areas of the root, are soft or leathery and are not cavitated. (ii) Advanced root lesions involve large surface area or cavity (5 mm square or larger). As a result of periodontal disease, the root surface becomes exposed to the oral cavity. Once decay sets in, the enamel is penetrated, and the soft vulnerable dentine is affected. This may be followed by extension into the soft pulp and the sensitive nerve fibres within it.

Prevention

For these patients the prevention and treatment of caries will become an essential part of their oral health needs. The rates of progression and reversal of coronal and root carious surfaces were low among community-dwelling elderly people using fluoride toothpaste [27]. Remineralisation of available tooth surfaces occurs with the use of fluoride toothpaste [28]. It is infrequently used in most developing countries compared to developed countries where it is widely used [18] (Box 1).

Box 1 Prevention of Caries

i. Oral hygiene.
   (a) Regular brushing, use of soft brushes, brushing in a gentle circular manner and rinsing with water frequently. Use of nonabrasive dentifrice brush after each meal
   (b) Regular flossing
ii. Use of dental sealants.
iii. Fluoride topical application, use of fluoride toothpaste.
iv. Low intake of sugar, acid foods and beverages.
v. Medications that are acidic, aspirin and vitamin C if chewed or held in mouth before swallowing can cause erosion.
vi. Discourage use of tobacco and alcohol.
vii. Regular dental check-ups.

Information sources: Zero et al. [29]

Periodontal Disease

Periodontitis has worldwide prevalence and affects individuals of all ages but is most common in the elderly. In the United States, up to 70% of adults have at least mild periodontitis, and gingivitis is highly prevalent [30]. Its prevalence increases with age from 6% in the 25–30 year group to 41% among those 65 years or older [31]. 75.1% of 70- and 80-year-olds had attachment loss of 3 mm or greater, and in them a mean of 4.7 teeth was affected [32]. Periodontal disease is associated with diabetes and cardiovascular diseases which is the major cause of death in the elderly [33]. Diabetes is a known risk factor for periodontal disease which can impair glycaemic control and set off diabetic complications [34]. There is a strong relationship between periodontitis and increased risk of developing cardiovascular disease [35, 36]. Increased mean of carotid intima thickening and periodontitis is an indicator of early atherosclerosis [37]. It can trigger the development of other systemic conditions that affect the elderly, such as cerebrovascular disease, rheumatoid arthritis and dementia [38, 39]. The risk factors for periodontitis are shown in Box 2.

Box 2 Risk Factors: Periodontitis

Poor nutrition
Clenching and grinding the teeth
Ill-fitting dental restoration

(*continued*)

Box 2 Risk Factors: Periodontitis (continued)
Tobacco smoking or chewing
Systemic disease, e.g. diabetes and histiocytosis
Fillings that become defective
Medications – anticonvulsants, steroids, immunosuppressive therapy, oral contraceptives
Information sources: Kinane and Marshall [40]

The gingiva may become swollen, tender and red and may bleed while brushing the teeth. There may be an unpleasant taste in the mouth as well as bad breath and pain while eating or chewing. Pus may be seen between the teeth, and the teeth may become loose. Exposure of the root surfaces increases sensitivity to heat and cold.

Management

Prevention

Factors relating to the prevention of periodontitis are shown in Box 3.

Box 3 Prevention of Periodontitis
Regular brushing using soft brushes
Brushing after meals and regular flossing
Making use of good mouthwash
Regular dental check-ups (6–12 months)
Improved mechanical and chemical plaque control
Avoid sugar and nutritional supplements
Local antiseptics and systemic antibiotics
Information sources: Jeffcoat [30] and Meletis [9]

Treatment

The treatment of older adults who are well is similar to the younger adults with emphasis on reducing the impact of risk indicators [41]. The physician and dental personnel should be in communication in order to determine the medical and drug histories [41].

Tooth Wear

The proportion of pathological tooth wear in the 65 years and older people is three times that seen in people aged 26–30 years [42].

Prevention

Risk factors for tooth wear include food with high acid content, citrus fruits (oranges, lemons, lime, grape fruit), fruit jams, vinegar, pickles and intrinsic acids –GORD. Unlike the prevention of caries, the prevention of tooth wear is largely individualised. Even though abrasion and attrition are individual based, erosion however has certain features somewhat akin to caries in its prevalence as well as in its relationship to diet [43]. The cause of erosion is largely linked with high consumption of soft drinks both juice and carbonated drinks [44]. It is well known that it is the frequency of acid exposure and the length of time the acids are present in the mouth that are important. Thus the consumption of acid foods should be in moderation, and intake should be at meal times [45]. The drinking of milk or eating a hard cheese soon after an erosive beverage may produce hardening of the enamel [46, 47].

The pattern of drinking an erosive beverage is significant especially when the drink is swished around the mouth before swallowing. It has been shown that drinking through a straw reduced the potential for tooth erosion from acid drinks [48]. Saliva and pellicle play an important role in the protection of the tooth substance against acid attack [43]. Chewing gum containing carbamide is said to raise the salivary pH and thereby reduce the erosive effect of acid in the mouth [43]. There are other preparations which increase saliva for patients including those with dry mouth. The use of sugar-free chewing gum and fluoride-containing carbamide is recommended [43]. Toothbrushing after an erosive challenge will produce more tooth wear. It has been shown that resistance to abrasion develops but not till 60 min has elapsed after the acid challenge [49]. The timing of the toothbrushing is relevant. Thus it is not advisable to brush the teeth soon after consuming beverages. Fluoride dentifrices with neutral pH may help to harden the softer enamel, and application of a dentine

binding or sealant to worn or eroded teeth may provide some protection [45].

Oral Cancer

Men are affected twice as often as women. Smoking and other forms of tobacco use account for 75% of oral cancers. Another risk factor is alcohol. In the United States, overall 10.5 adults per 100,000 will develop oral cancer, increasing with age, peaking between 60 and 70 years [50]. Oral cancers account for nearly 8000 deaths per year, and more than half of these occur at an age of 65 years and over [8].

It may begin as a painless ulcer in the lips, gum, tongue or in the inside of the mouth that does not heal and may bleed easily. Early sign is a white patch (leukoplakia) or a red patch (erythroplakia) on the mucosal lining of the mouth. The common sites are the margin of the tongue, cheeks, lower lip and floor of the mouth. Usually it is painless at the onset; pain and paraesthesia are late symptoms. There may be loss of feeling and numbness together with difficulty in chewing and swallowing food. A tissue biopsy will be necessary to confirm the diagnosis of oral cancer.

Edentulism

In the United States, people over the age of 65 years had an average of 18.9 remaining teeth, and 27.2% were toothless [51]. Edentulism increases with age and ranges from 8.4% in the 55–64 year age group to 19.7% in the 75 years and older with 31.5% being females and 9.6% males [52]. However the prospect of losing teeth with ageing is diminishing in developed countries because of better access to dental care, effective treatment and better nutrition. A research group found nine risk indications for tooth loss, and these include age, male gender smoking, lack of professional management, poor oral hygiene, diabetes, hypertension, cancer and anterior tooth type [53]. The most important cause of tooth loss in developed countries is periodontitis.

Tooth loss adversely influences eating habits and difficulty in food intake [54, 55]. Chewing becomes affected. The edentulous person tends to eat soft food, and foods such as meat, poultry and vegetables tend to be harder to chew. Altered eating habits lead to impaired nutrition; as a result, various health problems can occur. Impaired chewing also causes inadequate mixing of food with saliva and the enzymes in the saliva necessary for digestion.

The facial appearance of the person may be altered. Speaking may be affected. Edentulism has been linked with a number of diseases and medical conditions. Complete edentulism can substantially reduce the quality of life, self-image and daily functioning. There is considerable evidence to support a relationship between mastication and physical function [56]. Reduced dentition without replacement of the missing teeth has been shown to reduce the physical index of quality of life to the same extent as cancer or renal disease [57]. Prostheses can improve the chewing abilities. Teeth can be replaced by removable dentures (partial or full), bridges or implant-supported crowns. The type of replacement will depend on the health of the remaining teeth, gums and alveolar ridges.

Impact

Oral health and general health are closely linked, and poor oral health negatively impacts on general health especially in the elderly [11]. Oral health is one of the most influential factors in ill health involving ill health in a vicious cycle and terminating in impaired QoL. As age advances, multiple system conditions become more prevalent leading to impaired systemic and oral health influencing elderly person's QoL [58]. Chronic conditions can adversely affect self-care and have an impact on oral and general health [3]. The oral cavity is harmed directly or indirectly by systemic diseases, for instance, altering salivary flow which plays an important protective role in the mouth [3].

At the global level, dental caries and periodontal diseases contribute to considerable health problems in the majority of countries, and oral problems are high in low-income countries, and access to health care is poor [18]. In developed

countries, oral services are available; however the use of such services is low among older people [18]. Inadequate nutrition, illiteracy or low education level, low socioeconomic levels and minorities are at high risk of oral disease together with financial constraints, lack of family support and inadequate transportation facilities [10].

There is a significant interaction between oral health and nutrition. Oral disease and dysfunctional dentition lead to dietary alterations resulting in nutritional imbalances [37]. Improving oral will improve QoL through improved nutrition and greater comfort [3]. Oral health often declines with age with increased occurrence of caries, periodontal disease [9] and dry mouth, and the elderly may show increased sensitivity to drugs used in dentistry. The final stage of caries and periodontal disease if not resolved early results in edentulism [9]. Individuals who had no dentition were 4.6 times more likely to be malnourished [59]. The prevalence of periodontitis increases with age [31]. The loss of teeth may cause changes to the physical appearance and loss of self-esteem [60]. There is a strong interaction between periodontitis and an increased risk of developing cardiovascular disease [35, 36] (Box 4).

Box 4 Key Points

It is crucial; the management of oral care needs of the elderly will require the close cooperation of the primary care physician and the dental professional.

Oral health is an essential component to an elderly's general health and quality of life [6, 7].

With older adult living longer and able to retain more of the teeth, they are at risk of developing caries [21, 22].

Periodontitis is associated with diabetes and cardiovascular diseases which is the major cause of death in the elderly [33].

Tooth wear in the 65 years and over is three times that seen in people aged 26–30 years [42].

Tooth loss adversely influences eating habits and difficulty in food intake [54, 55].

Box 4 Key Points (continued)

Prosthesis can improve the chewing habits.

When prescribing bisphosphonate drugs or giving them injections, consider dental referral for people at increased risk, for instance, the elderly.

Multiple Choice Questions

1. The following statements in relation to oral health in the elderly are true, EXCEPT:
   A. The elderly often have problems such as impaired mobility in accessing health-care delivery system.
   B. Chewing, eating habits and nutritional state can compromise oral health.
   C. The elderly do not require special attention in relation to oral health care.
   D. Oral care needs of the elderly need close cooperation of the primary care physician and the dental professional.
2. The following are true relating to oral problems in the elderly, EXCEPT:
   A. There are high levels of oral disease in nursing home residents due to poor health status and the great impact of dementia.
   B. In the elderly, the exposed root surfaces in combination with compromised health status and multiple medications increase the risk of root caries.
   C. Oral organisms have been the source of infection of the endocardium, vertebrae, prosthetic joints and meninges among others.
   D. Periodontitis affects individuals of all ages but is uncommon in the elderly.
3. The following relating to oral problems in the elderly are true, EXCEPT:
   A. Toothbrushing after an erosive challenge will produce more tooth wear.
   B. The use of sugar-free chewing gum and fluoride-containing carbamide is not recommended for tooth wear.
   C. Smoking and other forms of tobacco use account for 75% of oral cancers.

D. The prospect of losing teeth with ageing is diminishing in developed countries because of better access to dental care.

MCQ Answers

1 = C; 2 = D; 3 = B

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Oral-Related Disorders

91

Contents

Abstract

The prevalence of awake bruxism is about 20% among the adult population and that of sleep bruxism is 8% of the population. Temporomandibular disorders (TMD) characterise a number of disorders often painful with different causes resulting in dysfunction of joint and/or muscles of mastication. Myofascial pain is estimated that about 25% of the entire population have internal derangement and is usually treated with non-surgical methods. Osteonecrosis of the jaw (ONJ) is characterised by exposure and necrosis of areas of the jaw. The true incidence of ONJ in patients on bisphosphonates (BP) is not known. This review discusses the mechanisms and management of some of the related oral disorders such as bruxism, temporomandibular dysfunction, myofascial pain and osteonecrosis of the jaw.

Keywords

Awake bruxism · Sleep bruxism · Temporomandibular disorders · Myofascial pain · Osteonecrosis of the jaw

Introduction

The oral cavity, masticatory muscles and the temporomandibular joint are important anatomical sites and play an important role in a number of oral disorders.

Clinical Manifestations

Bruxism

Bruxism is characterised by grinding or clenching of the teeth which usually occurs during sleep (sleep bruxism) and has been categorised as a

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_91

sleep disorder [1] but it can also occur during wakefulness (awake bruxism) [1]. The prevalence of awake bruxism is about 20% among the adult population and that of sleep bruxism is 8% of the population [1]. The pathogenesis is unclear, but it has been postulated that it could be due to occlusal factors although there is little evidence to support this. It appears to be regulated centrally [2] and modulated by various neurotransmitters [3]. It has been associated with a varied number of neurological and psychological disturbances and drugs [4]. It has also been shown that genetic factors may have a role in the generation of bruxism in children and adults [5]. It would appear that bruxism is a multifaceted problem. The likely signs of bruxism are tooth wear, loose teeth, chipping of teeth, sensitive teeth and receding gums with periodontal pockets. The patient may complain of headaches, sore muscles and pain and other problems involving the temporomandibular joints.

Management

Hot packs, night mouth guards or splints and muscle relaxants together with stress relief and jaw exercises are advised.

Temporomandibular Joint

Temporomandibular disorders (TMD) characterise a number of disorders often painful with different causes resulting in dysfunction of joint and/or muscles of mastication. TMD jaw pain has been self-reported by 30% of the general population [6], and the prevalent rates of difficulty in jaw opening and jaw clicking have been estimated at 0.3% and 1.8% [7] and 9% and 4% [6], respectively. There are no gender and age differences in the prevalence of opening, clicking, grinding and clenching [8], and in older subjects, subjective symptoms are more frequent than in the younger [9]. Review of the literature had revealed that TMD are less often seen in the elderly or at the same rate as in all adult groups [10].

Knowledge of the anatomy is important for the proper understanding of the temporomandibular disorders. The temporomandibular joint (TMJ) is a ball-and-socket joint, and the articular surfaces are the temporal bone and the condyle of the mandible and are enclosed in a capsule. Separating the articular surfaces is the meniscus, a fibrous saddle-shaped structure. Posteriorly, the meniscus is contiguous with posterior attachment tissues (bilaminar zone) which plays an important role in allowing the condyle to move forwards [1]. When the mouth opens, the condyle slides forwards beneath the articular eminence, and the intermediate zone comes between the condyle and the articular eminence [11]. When the mouth is fully open, the condyle may be beneath the anterior band of the meniscus [11]. When the mouth is closed, the posterior band of the meniscus lies immediately above the condyle. The physiology of the structures that constitute the TMJ, the cartilage, bone, the synovium, synovial fluid and the ligaments is regulated by biochemical and biomechanical processes [12].

The disorders of the TMJ can be considered in two categories: (i) intracapsular disorders – displacement of the articular disc, osteoarthritis and inflammatory arthritides, e.g. rheumatoid arthritis and synovitis, and (ii) extracapsular disorders, involving the muscles of mastication (masseters, temporalis and the pterygoids) with myofascial pain.

TMJ Dysfunction

In internal derangement of the TMJ, the posterior band of the meniscus is displaced anteriorly and is in front of the condyle [13]. Four types have been described [14], and the two more commonly occurring are the anterior disc displacement with reduction and anterior disc displacement without reduction [15]. In the former, the posterior band remains anteriorly in front of the condyle as the meniscus slides anteriorly. When the condyle reaches a certain position, the displaced posterior band returns to its normal position [11]. In the anterior displacement without reduction, the meniscus remains displaced anteriorly at full mouth opening, and the patients often cannot open their mouth fully [11].

The pain may vary in severity from mild to severe and is felt usually in the joint but may be felt in the surrounding structures. The pain is

usually made worse by clenching and chewing. There is tenderness over the joint, and often a clicking or popping sound may be heard when the mouth is opened or closed. There may be a grating sound at times and difficulty in opening or closing the mouth completely. With disc displacement with reduction, the opening of the mouth is limited often accompanied by deviation of the jaw to the affected side until a pop sound occurs [16]. Displacement without reduction occurs when the clicking sounds disappear but limited opening persists [17].

Diagnosis

In patients with anterior displacement with reduction, the only symptom may be a clicking or popping sound heard when the mouth is opened [13] or a lock is felt. Pain may occur when chewing hard foods. Apart from the patient, others may hear the sound. In the case of anterior displacement without reduction, there is no sound but mouth opening is reduced, less than the widths of the index, middle and ring fingers (<30 mm intercisal width) [13]. The patient often wakes up unable to open the mouth fully, and closing or protruding the jaw against resistance aggravates the pain [13]. Capsulitis, that is, inflammation of the tissues surrounding the joint (synovium, tendons, ligaments), can occur with either type of derangement, or it can occur spontaneously as a result of arthritis, infection and trauma. TMJ dysfunction is best evaluated by MRI for disc location and is essential because the presence of a displaced disc is a crucial sign of TMJ dysfunction [17].

Management

Analgesics such as NSAIDs together with hot and cold packs and gentle muscle stretching exercises may be helpful. In the case of displacement with reduction, an anterior repositioning bite splint may be used [13] to position the mandible forwards and on the meniscus. Displacement without reduction may not require treatment, and analgesics [13] should suffice but may require arthroscopic or open joint surgery in extreme cases. Arthroscopic surgery has been reported as safe and effective in relieving pain and increasing the range of mandibular motion [16].

Myofascial Pain

It is estimated that about 25% of the entire population have internal derangement and are usually treated with non-surgical methods [18]. This results from spasm of the muscles of mastication and irregular tooth contacts, and stress may be the cause as in nocturnal bruxism. There is limitation in opening the mouth, pain and soreness of the muscles of mastication, tenderness, clicking and local twitch response in the affected muscle [19]. The patient may complain of headaches in the morning on awakening which improves during the day. Unlike that in anterior displacement without reduction, the clinician can, with gentle pressure, open the mouth further beyond the unaided maximum opening. Trigger points, restricted range of motion together with local twitch response to local stimulation, are characteristic signs of myofascial pain [20].

Osteonecrosis of the Jaw (ONJ)

Osteonecrosis of the jaw (ONJ) is characterised by exposure and necrosis of areas of the jaw. The true incidence of ONJ in patients on bisphosphonates (BP) is not known but estimates range from 1.2 [21] to 15% [22]. There is a strong association with BP but there is no evidence that they cause ONJ and may even occur after the cessation of BP. The mandible is more often affected than the maxillary in the ratio of 2:1. BPs are important drugs used in a wide range of bone diseases. They are commonly used in osteoporosis, in metabolic diseases like Paget's and in bone cancers such as multiple myeloma, metastatic breast and prostate cancers. About 95% of the cases of ONJ have occurred with BPs used intravenously and in high doses for cancer and in 5% of osteoporosis patients on low-dose BP therapy [23]. ONJ is caused by a number of factors, and osteoporosis and past dental history have significant roles, while BPs have a synergestic effect [24].

Prior dental surgery or extraction was reported in two-thirds of the patients and in the remaining it occurred spontaneously. It usually presents with pain in the soft tissues and swelling or a persistent

non-healing wound following tooth extraction or dental surgery [25]. The teeth may be loose and the bone may be exposed. The patient may remain asymptomatic for weeks or months, and when symptoms develop, it is often the result of dental work, for instance, tooth extraction that exposes the bone.

CTs and MRI demonstrate characteristic changes but generally after the onset the CTX (C-terminal telopeptide) or cross laps test is a good indicator. This is an automated blood test to detect the presence of C-terminal telopeptide from the breakdown of type I collagen and is a reliable serum marker for bone resorption [26]. BPs are derivatives of pyrophosphate and significantly reduce the rate of bone turnover primarily inhibiting osteoclastic activity. If there is excessive turnover as in active resorptive phase of Paget' s disease, the level will be high. With BPs, the turnover is reduced and hence the levels will be low [27]. The test has been recommended for monitoring the bone turnover in osteoporotics on BPs. It gives an indication of the effects in 6 weeks which is very much sooner than the bone mineral density (BMD) which takes a year [27]. The CTX test has also been used as an indicator of the risk of BP-associated ONJ in patients on BPs [28].

Impact

The quality of life of sufferers of bruxism is compromised by many issues. The adverse effects of bruxism are headaches, sore muscles and pain, earache, loose teeth and late sensitive teeth, and late manifestations are chipping of the teeth, tooth wear and temporomandibular disease. Sleep is disrupted and that of the spouse due to the noise of grinding teeth. Temporomandibular disorders (TMD) pose a significant threat to overall quality of life. Early intervention strategies are known to minimise the impact on QoL [29]. Basic functions such a chewing, swallowing and speaking may be impaired by pain and limitation of movements and thus may interfere with daily life activities [29] (Box 1).

Box 1 Key Points: Related Oral Disorders

Bruxism is characterised by grinding or clenching of the teeth which usually occurs during sleep (sleep bruxism) but it can also occur during wakefulness (awake bruxism) [1].

The likely signs of bruxism are tooth wear, loose teeth, chipping of teeth, sensitive teeth and receding gums with periodontal pockets.

Temporomandibular disorders (TMD) characterise a number of disorders often painful with different causes resulting in dysfunction of joint and/or muscles of mastication.

Myofascial pain results from spasm of the muscles of mastication and irregular tooth contacts and stress may be the cause as in nocturnal bruxism.

There is a strong association with bisphosphonates (BP) but there is no evidence that they cause ONJ and may even occur after the cessation of BP.

ONJ is caused by a number of factors, and osteoporosis and past dental history have significant roles, while BPs have a synergestic effect [24].

Multiple Choice Questions

1. The following statements are true in relation to oral problems in the elderly, except:
   A. Prosthesis can improve chewing abilities.
   B. Patient with bruxism may complain of headaches, sore muscles and pain and other problems involving the temporomandibular joints.
   C. Temporomandibular dysfunction is associated with pain on clenching and chewing with clicking or popping sound when the mouth is opened or closed.
   D. The temporomandibular joint is a hinge joint.
2. The following relating to osteonecrosis of the jaw (ONJ) are true, except:

A. There is a strong association with bisphosphonates but there is no evidence that they cause ONJ.
B. About 95% of cases of ONJ have occurred with bisphosphonates used intravenously and in high doses in cancer.
C. The CTX or cross laps test can be used as an indicator of the risk of bisphosphonates associated with ONJ in patients on bisphosphonates.
D. Prior dental surgery or extraction was reported in less than 10% of the patients with ONJ, and in the remaining 90%, it occurred spontaneously.

MCQ Answers

1 = D; 2 = D

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Oral Manifestations of Systemic Disease

92

Contents

Abstract

Many systemic diseases have oral manifestations and they must be recognised. This review will summarise the oral manifestations in the main groups of system diseases such as connective tissue, nutritional, haematological and gastrointestinal disorders and drugs.

Keywords

Systemic diseases · Oral manifestations · Connective tissue disorders · Vitamin deficiencies

Introduction

Many systemic diseases have oral manifestations and they must be recognised. Inspection of the oral cavity is often overlooked in the examination of patients with systemic diseases. It is an important site for diagnostic signs in the search for a cause in systemic diseases.

Clinical Manifestations

Connective Tissue Disorders

Systemic sclerosis: The incidence in patients over 75 years with systemic sclerosis is around 20 per million per year, and the peak incidence in white females is between 65 and 75 years and in white males over 75 years [1]. In cutaneous systemic sclerosis, the most striking are facial and digital (sclerodactyly) findings. The facial appearance becomes pointed and masklike, and the lips are thin and pursed with a reduced oral aperture. Numerous telangiectasias may appear on the

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_90

lips, tongue, face and chest. The late-onset SLE patients have severe lung involvement, but fewer old patients have digital ulcers [2] and a more aggressive disease [3], but despite this the disease remains stable in patients over 75 years [4].

Systemic lupus erythematosus: In the elderly, the female/male ratio is 2:1, and 10–20% of the cases occur in the elderly [5–7], and the disease is milder. The diagnosis is often delayed in the late-onset. The gum and buccal mucosa and the junction of the hard and soft palate are the usual sites for recurrent ulcers. They are typically painless. Malar rash, glomerulonephritis [5, 6] and arthritis occur less frequently in the late-onset SLE. Sicca symptoms, interstitial lung disease and serositis are other common manifestations in the elderly [5–7]. In the late-onset patients, antinuclear antibodies [6, 7], RA factor, anti-Ro/Sjogren's syndrome and anti-La antibodies are more common than in younger patients [5]. The treatment is the same as that of younger patients [6] and also depends on its clinical manifestations.

Sjogren's syndrome: The elderly often present with sicca symptoms. Approximately 40% of xerostomia in the elderly is due to Sjogren's syndrome, and the elderly account for up to 20% of Sjogren's syndrome [8]. A common problem is the dry mouth often accompanied by periodontal problems and grittiness of the eye. Patients often complain of burning oral mucosa, intolerance to acid foods and difficulty in swallowing (odynophagia) and in talking. There may be diminution of the sense of taste and smell. The dryness of the lips and mouth (xerostomia) makes chewing and swallowing difficult and promotes tooth decay and formation of calculi in the salivary ducts. Vaginal dryness is common in the elderly [9].

Nutritional

Vitamin deficiencies: A common clinical pattern of involvement of the oral cavity occurs with most vitamin deficiencies, namely, angular cheilitis and glossitis. Fissures appear at the angles of the mouth with subsequent healing and formation of scars. In B6 deficiency, the tongue is magenta and the inner lip vermillion. In niacin deficiency apart from the glossitis, the colour of the tongue is scarlet. The gums become swollen, spongy and friable and bleed easily in vitamin C deficiency. With severe vitamin C deficiency, there may be secondary infection and loosening of the teeth. Easy bruising and mucosal bleeding occur in vitamin K deficiency, and the usual presentation is epistaxis.

Haematological

In iron deficiency, the tongue and lips are pale and angular cheilosis occurs. There are atrophy and denudation of filiform papillae [10]. Atrophic glossitis is a nonspecific finding and has been associated with iron deficiency anaemia, vitamin B12 deficiency and various other conditions [11]. With B12 deficiency, the complaint is a burning sensation of the tongue, and the tongue is beefy red in colour. Other manifestations include aphthous ulcers, xerostomia, ulcerative gingivitis and detachment of periodontal fibres, amongst others [10].

With the haematological malignancies, the manifestation is one of easy bleeding. In acute leukaemia easy bruising, petechiae and haemorrhage are common skin and mucous membrane manifestations. The gums may be oedematous, painful with a tendency to bleed easily. These changes may be associated with infection of the periodontal tissues.

Gastrointestinal

Lesions within the jaws, oral mucosa or perioral tissues may sometimes be seen as manifestations of gastrointestinal diseases [12]. In gastro-oesophageal reflux disorder (GORD), the dentine is exposed as the result of erosion of the enamel. Other signs include xerostomia, palatal erythema, halitosis and water brash [11]. Unlike that seen in dental caries, the eroded area is a 'dished-out' area and is hard. In Crohn's disease, the oral manifestations may precede intestinal involvement. Oral manifestations occur in about 60% of the patients

with Crohn's disease and may be the first sign in 5–0% of cases [13]. There are diffuse painful gingival, labial and cheek mucosal swelling with cobble stoning of the affected cheek mucosa [14], deep linear ulceration, 'snail track' ulcers on an erythematous base and localised mucogingivitis [11]. Aphthous ulcers, mucosal tags and angular cheilitis may be seen [15]. In ulcerative colitis, angular cheilitis and aphthous ulcers occur in about 5–10% of the patients [15]. The clinical differentiation of the oral changes between Crohn's disease and ulcerative colitis may be indistinct with overlapping clinical features [12]. The differential diagnosis includes nutritional deficiencies, side effects of drugs, infections and other inflammatory conditions [14].

Endocrine

In Addison's disease diffuse oral pigmentation occurs.

Drugs

With medications and group of medications, several patterns of disease have been identified, and oral findings are helpful in their identification [16]. The clinical patterns of adverse drug reactions of the oral cavity include xerostomia, swelling, nonspecific ulceration, specific ulceration, gingival enlargement, vesiculobullous lesions and ulcerative mucositis [16]. There is a higher risk of xerostomia in the elderly due to the larger amounts of medications. Medications such as phenytoin, nifedipine and cyclosporine predispose to gingival overgrowth, and immunosuppressive therapy may predispose to periodontal destruction [17] (Box 1).

Impact

Oral health and systemic health are closely linked [18], and poor oral health negatively impacts on general health especially in the elderly. The oral cavity is the site of infectious and inflammatory disease such as periodontitis, and there is increasing evidence to indicate it to be linked to diabetes mellitus, cardiovascular disease [18, 19] and atherosclerosis [20]. Many systemic diseases have oral manifestations [18, 21]. The primary care physician and the dental professional must be familiar with these for appropriate treatment and management of older patients with these conditions.

Box 1 Key Points. Oral Manifestations of Systemic Disease

The oral cavity is an important site for diagnostic signs in the search for a cause in systemic diseases.

Inspection of the oral cavity is often overlooked in the examination of patients with systemic diseases.

Approximately 40% of xerostomia in the elderly is due to Sjogren's syndrome, and the elderly account for up to 20% of Sjogren's syndrome.

A common clinical pattern of involvement of the oral cavity occurs with most vitamin deficiencies, namely, angular cheilitis and glossitis.

In iron deficiency the tongue and lips are pale and angular cheilosis occurs. There are atrophy and denudation of filiform papillae.

Lesions within the jaws, oral mucosa or perioral tissues may sometimes be seen as manifestations of gastrointestinal diseases.

With medications and group of medications, several patterns of disease have been identified, and oral findings are helpful in their identification.

Extending Matching Questions

1. Tongue magenta and inner lip vermillion
2. Gums swollen, friable and spongy and bleed easily
3. Burning sensation of tongue and beefy red in colour
4. Diffuse painful, gingival, labial, mucosal swelling with cobble stoning of the affected cheek

5. Dry mouth (xerostomia), grittiness of eye and difficulty in swallowing.
6. Lips thin and pursed with a reduced oral aperture, face masklike and numerous telangiectasis

The list above is oral manifestations. Choose the most likely cause from the list below. Each option can be used only once.

A. Systemic lupus erythematosus
B. Sjogen's syndrome
C. Vitamin C deficiency
D. Folate deficiency
E. Vitamin B6 deficiency
F. Systemic sclerosis
G. Niacin deficiency
H. Vitamin B12 deficiency
I. Crohn's disease

EMQ Answers

1 = E; 2 = C; 3 = H; 4 = I; 5 = B; 6 = F

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Index

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9