

Babak Tousi
Jeffrey Cummings
Editors

Neuro-Geriatrics

A Clinical Manual

 Springer

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*We dedicate this book to Camille
and Larry Ruvo.*

*Your passion and dedication to patients with
Alzheimer's disease created the Cleveland
Clinic Lou Ruvo Center for Brain Health.
Your commitment has led to care for
thousands of patients with brain disorders
and has spurred research that help treat and
prevent the tragedy of Alzheimer's disease,
Parkinson's disease, Huntington's disease,
multiple sclerosis, and other debilitating
brain diseases.*

*Babak Tousi dedicates this book to his
family whose guidance was always steadfast;
to Dr. Robert Palmer, Dr. Mark Frankel, and
Dr. Thyagarajan Subramanian who piqued
his interest in the geriatrics, geriatric
psychiatry, and neurology; and Dr. Jeffrey
Cummings who has never stopped being an
inspiring mentor.*

*Jeffrey Cummings dedicates this book to
Kate (Xue) Zhong.*

Foreword

This book is dedicated to my great friends Larry and Camille Ruvo. To honor Larry's father, Lou, who succumbed to Alzheimer's disease, Larry and Camille have dedicated themselves to bringing better care to patients with Alzheimer's disease, supporting their families, and advancing research. After founding Keep Memory Alive (KMA), they engaged Frank Gehry to design the dramatic building housing the Lou Ruvo Center for Brain Health; with this genius insight they have been able to attract worldwide attention to the remarkable program for patients with brain disorders they initiated in Las Vegas, Nevada. When Larry and I met, we realized that our Patients First goals were aligned and that Cleveland Clinic would be the optimal clinical partner for the Lou Ruvo Center. Since bringing the Lou Ruvo Center for Brain Health into the Neurological Institute, we have expanded the program to include Lou Ruvo Centers on the Cleveland Clinic Main Campus, Cleveland Clinic Lakewood Campus, and Cleveland Clinic in Weston, Florida. Our Alzheimer's disease and memory disorders group of specialists is now among the largest in the world. The Lou Ruvo Centers have established new standards of Patients First care, pioneered exciting new programs for caregivers, and advanced new therapies through their active clinical trial program. The research program of the Lou Ruvo Center is now the largest in the Cleveland Clinic Neurological Institute. Many of these advances are captured and presented in *Neuro-Geriatrics*. It is a great pleasure to endorse this volume that showcases much of what we have accomplished through our relationship with Larry and Camille and through the growth of the Cleveland Clinic Lou Ruvo Centers.

Neuro-Geriatrics captures many of the principles of the care philosophy and the commitment to quality care of the Cleveland Clinic. The centrality of the patient and caregiver experience, the use of research-based diagnostic criteria to support accurate diagnoses, the guidance of care by care paths, the commitment to evidence-based medicine, the reduction of practice variance through diagnostic and treatment algorithms, cost control by an expert decision-support framework, and the continuous translation of research advances into clinical practice are shared features throughout the Cleveland Clinic.

Neuro-Geriatrics presents these features as applied to the care of older adults with brain disorders. The aim of *Neuro-Geriatrics* is to facilitate dissemination of these best practices throughout the healthcare system.

The growth of the aging population in the United States and globally and the dramatic increase in age-related brain diseases demand that we develop innovative approaches to care of patients with chronic neurologic disease. *Neuro-Geriatrics* presents essential elements of meeting this demographic imperative.

The thorough discussions of neurodegenerative, vascular, and traumatic brain disorders provide a comprehensive approach to Neuro-Geriatric care. The diagnostic criteria, care paths, diagnostic and therapeutic algorithms, diagnostic and billing codes, and clinical pearls are unique features of *Neuro-Geriatrics*. They make this manual a user-friendly, helpful, care and teaching manual for clinicians.

The Cleveland Clinic takes pride in *Neuro-Geriatrics* as a means of enhancing care of geriatric patients with brain disorders by all practitioners.

Toby Cosgrove
President and CEO
Cleveland Clinic

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Disclaimer

Every effort has been made in this book to provide accurate and up-to-date information that is consistent with accepted standards of practice and use of medications in the elderly. Treatment of elderly persons must be individualized and doses and treatment strategies may differ for specific patients. The authors, editors, and publishers make no warranties that the information contained in *Neuro-Geriatrics* is free from error or will necessarily lead to the desired outcome. Side effects from pharmacologic treatment are common and often unpredictable. The authors, editors, and publishers disclaim all liability for damages resulting from the use of material presented in this volume. Readers are urged to pay careful attention to updated information, new guidelines from the Food and Drug Administration and other agencies, and the evolution of clinical practice standards.

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Dr. Cummings is interested in clinical trials, developing new therapies for brain diseases, and the interface of neuroscience and society.

Dr. Cummings completed Neurology residency and a Fellowship in Behavioral Neurology at Boston University, Boston, Massachusetts. US training was followed by a Research Fellowship in Neuropathology and Neuropsychiatry at the National Hospital for Nervous Diseases, Queen Square, London, England. Dr. Cummings was formerly Professor of Neurology and Psychiatry at UCLA, director of the Mary S. Easton Center for Alzheimer's Disease Research at UCLA, and director of the Deane F. Johnson Center for Neurotherapeutics at UCLA. He is past president of the Behavioral Neurology Society and of the American Neuropsychiatric Association.

Dr. Cummings has authored or edited 39 books and published over 700 peer-reviewed papers.

Neuro-Geriatrics: An Introduction

Jeffrey Cummings and Babak Tousi

The world's population is aging rapidly. The population 65 and over has increased from 36.2 million in 2004 to 46.2 million in 2014 (a 28% increase) and is projected to more than double to 98 million in 2060. The 85 and older population is projected to triple from 6.2 million in 2014 to 14.6 million in 2040 [1]. Globally, the number of people 65 and older will triple by mid-century, from 531 million in 2010 to 1.5 billion in 2050 [2]. With aging there is an inevitable increase in age-related disorders. Alzheimer's disease (AD) doubles in frequency every 5 years after age 65 rising from 1% of 65 year olds to 40–50% of those over 85 [3]. The number of persons with AD in the USA will rise from 5.2 million today to approximately 13.8 million by 2050; during the same period the world's AD population will increase from its current 35 million to well over 100 million if no intervention is found [4]. In the USA, dementia leads to total annual societal costs of \$41,000 to \$56,000 per case, with a total cost of \$159 billion to \$215 billion nationwide in 2010. The costs of AD exceed the annual cost of care of cardiovascular disease or cancer [5].

For Parkinson's disease, similar trends emerge. Approximately 630,000 people in the United States had PD in 2010, with prevalence likely to double by 2040. The national economic burden of PD exceeded \$14.4 billion in 2010 (approximately \$22,800 per patient). The population with PD incurred medical expenses of approximately \$14 billion in 2010, \$8.1 billion higher (\$12,800 per capita) than expected for a similar population without PD. Indirect costs (e.g., reduced employment) are conservatively estimated at \$6.3 billion (or close to \$10,000 per person with PD) [6]. Other neurodegenerative disorders, stroke, and many other neurologic diseases will experience similar age-related increases in numbers. New management strategies are needed to address the medical needs of this population. *Neuro-Geriatrics* provides expert guidance in the diagnosis and management of this burgeoning population.

Neuro-Geriatrics addresses two of the most important themes in modern medicine—neurology and geriatrics. Neurology and applied neuroscience have made remarkable progress in developing new diagnostic strategies with improved clinical criteria and integrated biomarkers that identify the underlying biology associated with specific clinical phenotypes [7]. These diagnostic criteria are provided

in each chapter conveniently captured in table form for ready reference. The criteria guide the required clinical observations as well as the biomarkers that may help define the underlying disease process. Accurate diagnosis is the basis for expert management and therapy. Even where specific symptomatic or disease-modifying therapies are lacking, a correct diagnosis facilitates prognostication, discussions with family, and assessment of any associated genetic risks. When therapy is available, accurate diagnosis is the foundation of treatment implementation.

Neuro-Geriatrics is based on translational medicine with an emphasis on translating the most evolved research concepts into the practice of medicine [8, 9]. Magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG) positron emission tomography (PET), molecular imaging with amyloid-labeling ligands, electroencephalography (EEG), and electromyography (EMG) are all advanced technologies that contribute importantly to contemporary medicine. These biomarkers are incorporated into diagnostic criteria for the most current application of translational medicine. The forward march of neuroscience and the translational application of neuroscience discovery to improve patient care enhance the practice of neuro-geriatrics [10–12].

Neuro-Geriatrics presents care paths for each disease or condition with standards of care and decision-support algorithms for diagnosis and treatment. Care paths are an important means of approaching the architecture of care, defining needed actions (clinical assessment, laboratory studies, brain imaging), decision points, and treatment implementation and monitoring. Care paths link the evolving science of neurology and geriatrics to anticipated outcomes and costs of care. Medical systems and responsible practitioners are increasingly cost conscious and algorithms, through their standardized approach to the diagnostic process, assist in the goal of reducing or justifying costs. They provide the practitioner with justifiable and necessary actions, and they provide care leadership with a structure for anticipated costs of care. Care paths can be linked to outcomes and can be iteratively improved to insure optimal value to the patients for the care rendered and the costs incurred. Care paths provide a means of introducing evidence-based medicine and clinical guidelines into care; improve clinical effectiveness and risk management; facilitate care audits; improve multidisciplinary communication, teamwork, and care planning; support continuity and co-ordination of care across different clinical disciplines and sectors; provide explicit and well-defined standards for care; can improve care documentation; facilitate the dissemination of accepted standards of care; and provide a baseline for future care initiatives [13, 14].

Diagnostic and therapeutic algorithms are presented in nearly every chapter of *Neuro-Geriatrics*. The purpose of algorithms is to allow immediate guidance for clinical decision making—clinical observations to be made, tests to be ordered, differential diagnosis to be considered—and to standardize the process of diagnosis and treatment. Algorithms serve a mentoring function, improve outcomes, and reduce variance among practitioners [15]. Practice variance is undesirable, increases costs, and compromises patient outcomes. Clinicians are increasingly pressured for time and rapid means of calling on expert decision systems to rapidly resolve diagnostic and therapeutic questions have great value as time-saving devices that

maintain or improve quality. *Neuro-Geriatrics* anticipates the many demands of contemporary medical practice.

Evidence-based medicine (EBM) is a cornerstone of contemporary medicine and *Neuro-Geriatrics* incorporates this approach in every chapter. Diagnostic criteria are based on retrospective studies or prospective validations and incorporate expert opinion where data are lacking. Practice guidelines incorporating EBM approaches are structured into the care paths and these paths provide a framework for introducing future guidelines and new EBM care strategies [16–19].

Therapeutic recommendations are based on clinical trials and both efficacy and adverse events are presented to allow the clinician to consider the benefit/harm ratio for any intervention [17]. Nonpharmacologic recommendations for treatment are included where available [20]. Progress has been made in developing new therapies specifically for behavioral changes in neurological diseases. For example, the combination of dextromethorphan/quinidine (Nuedexta™) has been approved for pseudobulbar affect (PBA) in neurological disorders, and pimavanserin (Nuplazid™) is approved specifically for hallucinations and delusions in PD [21, 22]. Appropriate use of these new agents is presented in *Neuro-Geriatrics*.

Older patients are more likely to have multiple comorbid conditions than younger patients. The combination of AD and cerebrovascular disease is common and many AD patients have mixtures of AD and Lewy body pathology [23, 24]. “Pure AD” is relatively uncommon. Vascular disease may complicate other late-onset disorders such as PD and other movement disorders. *Neuro-Geriatrics* draws attention to the importance of considering comorbidity in the management of older patients.

Genetics has made tremendous strides in the past few decades and now has meaningful—though still limited—clinical application. In *Neuro-Geriatrics* we include genetic information where it may be helpful in the diagnostic assessment (e.g., inherited forms of frontotemporal dementia, apolipoprotein E epsilon 4 [ApoE-4] in AD, early onset AD, etc.) or in treatment (polymorphisms that affect drug metabolism) [25, 26]. The approaches in *Neuro-Geriatrics* pave the way for precision medicine and the use of biomarkers including genetics to choose the right medication for the right patient, improving efficacy and reducing side effects.

Neuro-Geriatrics strives to be a person-centric guide to care. Person centricity must guide all care decisions. Involvement of the patient and their families in care decisions will insure that an alliance for care has been established and optimal outcomes promoted [16, 27]. Patient reported outcomes are increasingly included in clinical trials to insure that the goals of the patient are also the goals of the drug development program [28]. *Neuro-Geriatrics* provides a framework for considering person-centricity in every step of the care path.

Brain health is the counterpoint of brain disease. Clinical presentations reflect the balance between brain disorders and the individual features of the person affected including their brain reserve and resilience to disease impact [29, 30]. *Neuro-Geriatrics* includes recommendations for integrating brain health strategies into the management of geriatric brain disorders including online resources such as Cleveland Clinic Lou Ruvo Center for Brain Health healthybrains.org. Brain health and brain reserve are prevention-related concepts to be incorporated into the care of all patients.

Neuro-Geriatrics has a standard approach to each disorder and includes the following features for the reader's convenience:

- Diagnostic criteria
- Diagnostic algorithm (rendered in green)
- Examples of results from commonly used brain imaging approaches wherever possible
- Therapeutic algorithm (rendered in blue)
- Treatment recommendations
- ICD-10 diagnostic codes to facilitate documentation
- Clinical pearls of important facts about the disorder

Neuro-Geriatrics presents a new approach to the care of older patients with neurological disease. We sincerely hope that our goal of improving the care of patients and supporting families will be realized by all who incorporate the approaches of this volume into their clinical practice.

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Chapter 1

Office Approach to Neurological Disorders in the Elderly

Po-Heng Tsai and Dennys Reyes Candedo

Clinical Pearls

- Depression produces a retrieval deficit type memory disorder.
- Normal aging affects memory retrieval more than memory storage.
- Late-onset changes in behavior are usually neurologically-based.

Introduction

The growth of the elderly population demands that all practitioners be prepared to care for aging patients. Most geriatric neurological assessments are completed under the current healthcare system's constraints of time and money. Therefore, a directed approach that relies on a focused history and examination guided by the chief complaint is required. This chapter will demonstrate an evaluation approach for elderly patients based on the common neurological complaints in the office setting.

Obtaining the History of a Neurological Complaint

Memory Difficulties

Millions of Americans have dementia, including approximately 5.4 million people are living with Alzheimer's disease (AD) [1]. Because age is one of the most important risk factors for the development of dementia, the number of Americans with

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dementias will grow as the population ages. Unsurprisingly memory concern is one of the most common presenting complaints in geriatric patients, and detection of cognitive impairment is part of the Medicare Annual Wellness Visit [2].

Evaluation for memory issues should begin with a detailed history. The onset along with the progression of the patient's main complaints should be prioritized since it will narrow the differential diagnosis. For example, an insidious onset of cognitive difficulties would suggest a neurodegenerative process whereas an acute or subacute onset might imply a cerebrovascular, traumatic, epileptogenic, delirium, central nervous system (CNS) infectious disorder or other non-neurological medical problems such as dehydration or urinary tract infection. A rapidly progressive pattern of cognitive decline will lead to the consideration for Creutzfeldt-Jakob Disease (CJD). It is also important to investigate for accompanying symptoms that could help differentiate various types of dementing illness including (1) personality, behavioral, and language changes that suggest frontotemporal dementias and primary progressive aphasia; (2) psychiatric features including depression for "pseudodementia" of depression; (3) sleeping difficulties including obstructive sleep apnea symptoms or dream enactment behaviors that are frequently associated with synucleinopathies such as Lewy body disease (LBD); (4) visual or auditory hallucinations that could be seen in psychiatric disorders or LBD; or (5) urinary dyscontrol or incontinence and walking difficulties associated communicating hydrocephalus or parkinsonian spectrum disorders.

When evaluating memory difficulties, it is important to have a close family member or caregiver present for collateral information; the patient might have difficulty providing a detailed history due to cognitive impairment or lack of insight. Preferably the patient and the collateral informant are interviewed, as the caregiver in the presence of the patient may feel uncomfortable relating personal information such as embarrassing behaviors or safety concerns including those associated with driving.

Next, address the patient's instrumental activities of daily living (IADLs) including financial/medication management, computer and cell phone adaptation, use of transportation, and household chores. If IADLs are preserved, it is less likely the patient will show difficulties with basic activities of daily living (BADLs) although inquiries should address mobility, bathing and showering, dressing, self-feeding, personal hygiene, and grooming. Impairments of ADLs provide clues regarding the degree of cognitive impairment and are required for the diagnosis of dementia [3].

Reviewing medications is important to identify drugs that could adversely impact cognition such as anti-cholinergics. Level of education of the patient should be queried given that a lower level of education has been associated with a greater risk for dementia and could affect the patient's performance on cognitive assessments [1]. A thorough memory-related history is followed by the mental status examination (described later).

Headache

A headache history should uncover the pattern of symptoms (location, quality of pain, severity, associative symptoms, and alleviating/exacerbating factors) that enable identification of the cause and rule out alternative conditions such as

meningitis or intracranial hemorrhage. Tension headaches usually present bilaterally with non-pulsatile pain of mild to moderate intensity, while migraine headaches tend to be one-sided with moderate to severe pulsating pain that is associated with nausea, vomiting, and sensitivity to light and sound. Migraines in the elderly may be bilateral and are less likely to have these associated features. Lateralized pain presenting with unilateral autonomic symptoms (lacrimation, conjunctiva injection, rhinorrhea, and nasal congestion) suggests trigeminal autonomic cephalalgias, which include cluster headaches and paroxysmal hemicranias.

Secondary causes of headaches increase with age. Features requiring prompt assessment would include a thunderclap onset, positional pain with worse symptoms while lying flat, associated neurological deficits, systemic signs and symptoms (fever, chills, myalgia, weight loss, etc.), nuchal rigidity, visual obscurations, and change in mental status or cognition [6]. These may indicate infection or neoplastic disease or subarachnoid hemorrhage.

Neck and Back Pain

Even though degenerative changes in the spine are almost ubiquitous on imaging studies in people age 65 and up, most patients are not significantly symptomatic [4]. When patients do present for evaluation of neck and back pain, history should focus on the description of the pain that includes the onset, localization, quality, intensity, radiation, frequency, duration, progression, alleviating and aggravating factors, and associated symptoms. The constellation of symptoms helps identify potential etiology. Another important aspect of assessment should focus on identification of “red flags” that could signal systemic process or medical etiologies, which necessitate prompt evaluation: suspicion for infection (e.g. fever, history of intravenous drug use, recent spinal instrumentation/puncture, immunocompromised status, etc.), history of malignancy, suspected vertebral compression fracture (antecedent trauma, chronic corticosteroid use, etc.), new bowel or bladder incontinence, saddle anesthesia, and significant motor deficits.

Weakness

When a patient presents with complaints of weakness, it is essential to query the pattern of weakness, which aids in the differential diagnoses. Presenting symptoms such as difficulty arising from a chair, climbing stairs, walking and using the arms above the head might be indicative of a myopathic disorder. The distribution of weakness in most myopathies is typically proximal, involving the neck, limb girdle, humeral and femoral musculature. Muscle weakness outside of this typical myopathic distribution could help identifying specific etiologies such as the involvement of finger flexors (distal muscles) and quadriceps femoris (proximal muscle) commonly found in inclusion body myositis.

Neuropathic process typically presents with distal weakness with complaints of clumsy hand and finger movements, decreased grip strength, difficulty standing on toes and heels, or foot drop. Frequently, neuropathic processes are associated with sensory symptoms of numbness, tingling, or pain. The presence of weakness without sensory complaints might suggest an isolated motor neuropathy or a motor neuron disease such as amyotrophic lateral sclerosis (ALS). The latter is nearly always asymmetric starting in either arm, leg or bulbar muscles accompanied by cramps and fasciculations and with preserved autonomic functions.

When weakness involves bulbar muscles such as the presence of ptosis, diplopia, hypophonia, and dysarthria, especially if the symptoms fluctuate over the course of the day or worsen with prolonged activities, it points towards a neuromuscular junction disorder like myasthenia gravis. Double vision should be further characterized by determining from the patient whether it can be corrected by covering one eye because a monocular diplopia (i.e. double vision persisting with one eye closed or covered) will most likely be related to intrinsic ocular disease (e.g., lens dislocation). Asking whether the images are duplicated horizontally or vertically could orient the clinician in regard to the possible eye muscles involved.

Tingling, Numbness, and Burning Pain

Neuropathic disorders constitute an important disease group and a frequent source of complaints in the elderly population. The initial approach with these patients is to determine not only if the symptoms are purely sensory, purely motor or both, but to clarify the onset, duration, pattern, and evolution of the symptoms.

The duration of symptoms between days to 4 weeks is considered acute; 4–8 weeks is subacute; and greater than 8 weeks is considered chronic. Patients presenting with subacute or acute sensory and motor symptoms, especially if the symptoms are symmetric and rapidly progressive, should raise concern for Guillain-Barre syndrome. If symptoms are isolated to one limb, then the diagnosis of radiculopathy, plexopathy, vasculitis or a compressive mononeuropathy is more likely.

The idiopathic sensory or sensorimotor polyneuropathy and diabetic neuropathy are the most common neuropathy seen in clinical practice [5]. For idiopathic polyneuropathy and diabetic polyneuropathy, patients will usually present with distal numbness, tingling or burning pain affecting initially the feet and eventually the fingers and hands. Another painful form of diabetic neuropathy is the lumbosacral radiculopathy (also known as diabetic amyotrophy), which can present with abrupt onset of hip or thigh pain that may precede weakness by hours or days.

Careful family, occupational and toxic exposure histories (i.e. heavy metals, medications such as chemotherapeutic or anti-infective agents, and alcohol) and questions geared to uncover an endocrinopathy or other systemic condition like cancer, human immunodeficiency virus (HIV) infection, vitamin deficiency/toxicity, or collagen-vascular disorders are important in detecting clues for the possible

underlying neuropathic process. When suspecting a possible hereditary cause of peripheral neuropathy, it is important to inquire about foot deformities such as hammer toes and high arched feet in immediate relatives.

Peripheral neuropathy is sometimes associated with autonomic nervous system dysfunction, and patients could present with fainting spells or orthostatic lightheadedness, heat intolerance, or bowel, bladder or sexual dysfunction. Autonomic dysfunction in the absence of diabetes should trigger the consideration of other causes of autonomic neuropathy including amyloidosis, sarcoidosis, and paraneoplastic syndromes.

Tremor and Other Abnormal Movements

Tremor (see Chap. 20) is the most common abnormal involuntary movement in the adult population and is characterized by a rhythmic oscillation of one or more parts of the body including the head [7]. Most times, patient won't seek medical attention until the tremor interferes with their daily activities such as writing or eating. The upper extremities are more frequently affected than the head or the lower extremities, and in a minority there could be a voice tremor. Almost all involuntary movements are exacerbated by stress, excitement, fatigue or a variety of drugs including caffeine and are alleviated or would disappear during sleep.

The clinician should inquire about the onset and progression over time, correlation with activity or rest and asymmetry of symptoms at onset. Bilateral upper extremity postural or action tremor with a positive family history and improvement with alcohol is suggestive of essential tremor. Head and voice tremor can also characterize essential tremor. Tremor associated with Parkinson disease tends to occur unilaterally, at rest, is not responsive to alcohol, and is usually associated with other parkinsonian symptoms such as rigidity and bradykinesia. Special attention should be given to the patient's list of medications including dopamine blockers (antipsychotics, metoclopramide, prochlorperazine), lithium, and valproic acid to exclude drug-induced tremor or parkinsonism.

Gait Difficulties and Falls

When evaluating a patient presenting with gait issues and falls, the history should focus on eliciting the possible reasons for the complaints (see Chap. 21). Typically, the etiology is multifactorial and could encompass both neurological and non-neurological issues including musculoskeletal pain, visual impairment, vertigo, etc. The presence of vascular risk factors raises the possibility of cerebrovascular disease. Numbness and tingling with or without pain in the feet suggest peripheral neuropathy. It is also important to assess for the symptoms of parkinsonism, i.e.

presence of rigidity, slowness, and tremors. The classic triad of gait impairment, cognitive deficits and urinary incontinence leads one to consider normal pressure hydrocephalus (NPH) or cerebrovascular disease.

Examination of a Patient with Neurological Complaint

General Examination

As part of the general examination of the patients, pursuing an orthostatic fall of blood pressure will be helpful in cases where autonomic nervous system dysfunction is suspected. Inspection of the head with evidence of frontal balding, long narrow jaw and ptosis with wasting of the neck and temporalis muscles are typical findings for myotonic muscular dystrophy.

During general exam of the skin, the presence of rash with a butterfly facial pattern, eyelids heliotrope discoloration, or affecting the knuckles with periungual hyperemia and telangiectasia suggests rashes associated with dermatomyositis.

Within the cardiovascular system, the presence of cardiac arrhythmias including atrial fibrillation or valvular insufficiency would suggest a possible source of emboli in patients with cerebrovascular events. The presence of a carotid bruit may signal stenosis and occlusive cerebrovascular disease.

Examination of the spine involves evaluating for scoliosis or limited range of motion of the cervical or lumbar spine indicative of spondylitic changes. Spurling maneuver and straight leg raise test could reveal support for a radicular pain process. Evaluation of the lower extremities, particularly the feet for arch or toe abnormalities (e.g. high or flat arches, hammer toes) could provide evidence for a peripheral neuropathic process.

The Mental Status Exam

Mental status examination should focus on five key areas of cognition: attention, memory, language, visuospatial skills, and executive function. Attention is tested with digit span forward where the patient is asked to repeat a string of numbers of increasing length, which are produced by the examiner at one digit per second. Memory of newly learned material is tested by providing the patient with three or more words to register, and then asking the patient to recall the words after a delay. Semantic cues and multiple choices are provided after delayed recall to further distinguish between memory deficits due to retrieval (benefit from cueing) versus encoding (no benefit from cueing) difficulties (Fig. 1.1). Language examination should assess for fluency, comprehension, and repetition, which helps one to determine the type of aphasia a person may have (Fig. 1.2). For assessment of visuospatial function, the patient is asked to copy various figures or to draw a clock. Executive function could be assessed in various tasks including word list generation,

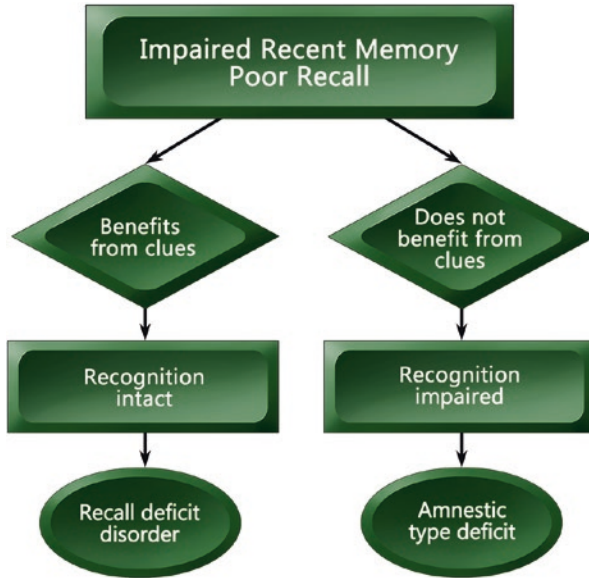


Fig. 1.1 Approach to memory disorders

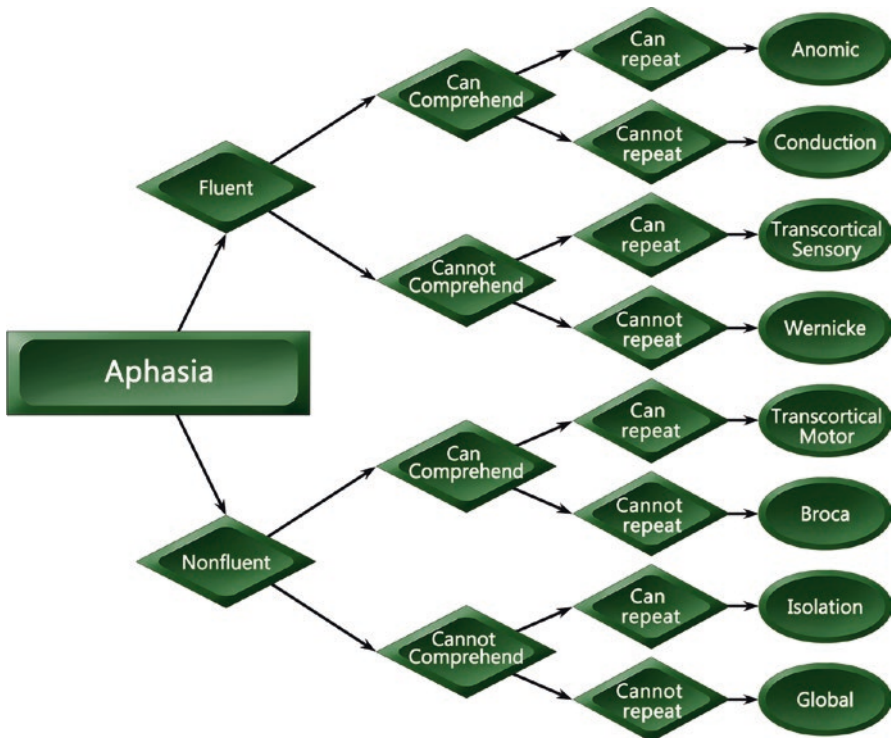


Fig. 1.2 Approach to aphasic disorders

abstraction, proverb interpretation, set shifting with alternating tapping, motor programming with Luria hand sequences, and response inhibition with Go-No-Go tests. The patient's cognitive profile assists in differentiating various types of dementing illness. For incidence, patients with Alzheimer disease tend to have encoding memory deficits while patients with vascular dementia have more executive dysfunction and retrieval memory difficulties.

Standardized scales such as Montreal Cognitive Assessment (MoCA) are available that encompass assessment of these key areas. The Alzheimer's Association recommends using the Memory Impairment Screen (MIS), the General Practitioner Assessment of Cognition (GPCOG), and the Mini-Cog in the primary care setting for cognitive assessment associated with an Annual Wellness Visit [2].

The Cranial Nerves Exam

Funduscopy examination allows visualization of the optic nerve (CN II); the presence of papilledema indicates increased intracranial pressure. Testing of eye movements (CN III, IV, and VI) is important to reveal ocular muscle weakness. In addition, decreased pursuit eye movements, especially with downward gaze, could suggest progressive supranuclear palsy whereas impaired upgaze, especially in conjunction with pupillary and convergence deficits ("Parinaud syndrome") could signal dorsal midbrain involvement. Ptosis or facial asymmetry (CN VII) can be observed without any overt maneuvers. Oropharyngeal muscle (CN IX and X) may manifest weakness with nasal voice, hoarseness or dysarthria when assessing speech. Voice distortion could be secondary to laryngeal dystonia or spasmodic dysphonia.

The Motor Exam

Motor examination begins with observation. Inspecting for involuntary movements such as tremor or fasciculations is the initial step, followed by appreciation of the muscle bulk and muscle tone. Myoedema and increased muscle bulk can be found in patients with hypothyroid myopathy. The motor strength scale (0–5) is the most useful tool grading the muscle strength of different muscle groups in the upper and lower extremities, and neck muscles as well:

- 0 = No contraction
- 1 = Flicker or trace of contraction but no movement of the joint
- 2 = Active movement with gravity eliminated
- 3 = Active movement against gravity but no additional resistance
- 4 = Active movement able to overcome some resistance but not full resistance
- 5 = Normal power; able to overcome full resistance

Semi-quantitative assessment aids in the differentiation of a myopathic versus neuropathic process, i.e. predominantly proximal versus distal weakness. The pattern of weakness is also helpful in distinguishing upper and lower motor neuron involvement: upper motor neuron pattern of weakness is usually more pronounced in the flexors of the lower extremities than in the extensors while extensors are weaker than the flexors in the upper extremities.

In addition to strength testing, it is important to evaluate for signs of parkinsonism. The facial gestures and eye blinking become relevant as well as assessing muscle tone, evaluating rigidity and differentiating it from spasticity. Cogwheel rigidity is a typical parkinsonian sign identified most easily with arm flexion and extension at the elbow but not limited to this joint. Paratonia or gegenhalten is a form of hyper-tonia with an involuntary resistance during passive movement, usually related to dementia. Maneuvers to assess for bradykinesia include finger tapping, hand movements, pronation-supination, toe and heel tapping, arising from chair, stride, arm swing, and freezing of gait.

Tendon Reflexes Exam

Common tendon reflexes evaluated during a clinic visit are the biceps (C5–C6), triceps (C7), and brachioradialis (C6) for the upper extremities, and the patellar (L2–L4) and Achilles (S1) reflex for the lower extremities (associated nerve root are indicated in the parentheses). Depending on the clinical scenario of the patient, it may be important to assess other reflexes such as jaw jerk to investigate trigeminal nerve dysfunction and to help distinguish an upper cervical cord compression from lesions that are above the foramen magnum. Reflexes are graded on a scale between 0 and 4:

- 0 = Absent
- 1 = Reduced (hypoactive)
- 2 = Normal
- 3 = Increased (hyperactive)
- 4 = Clonus

Plantar responses are assessed and graded as flexor (normal response), extensor (Babinski sign), or equivocal.

Tendon reflexes tend to diminish with age, and the presence of hyperreflexia would suggest central nervous system disorder. Unilateral hyperreflexia is a typical residual sign from hemiparesis related to stroke or other lateralized lesion. An absent ankle muscle stretch reflex can be found in cases of idiopathic sensory or sensorimotor polyneuropathy, S1 lumbar radiculopathies and demyelinating polyneuropathies. More widespread absence of reflexes can occur in patients with diabetic or demyelinating polyneuropathies.

The combination of motor and reflex examination allows differentiation of upper versus lower motor neuron processes. Upper motor neuron signs include increased muscle tone, hyperreflexia, and extensor plantar responses while lower motor neu-

ron signs consist of presence of fasciculation, decreased tone, and hyporeflexia. Signs of both upper and lower motor neuron involvement could be seen in motor neuron disease.

The Sensory Exam

Sensory examination during a clinic visit will include light touch, temperature, pain, vibratory and proprioception of the upper and lower extremities. The pattern of sensory loss could follow the distribution of a peripheral nerve or a nerve root dermatome, which helps with localization of lesions. Loss to pain, temperature, touch and vibratory stimulus in a stocking and/or glove distribution provide evidence for a sensory polyneuropathy. The presence of a sensory level suggests spinal cord involvement.

Posture, Stability and Gait Exam

The first feature to annotate during gait assessment would include posture of the patient with a descriptive evaluation of the curvature of the spine, head position, pelvic tilt, and flexion of knees and hip, which could reveal orthopedic issues impacting the gait. The patient's casual walk is observed noting initiation of gait, step height, stride length, width and rhythm, turning, coordination of upper and lower limbs (e.g. arms swing), and the ability to complete a tandem gait. A retropulsion maneuver ("pull test") is a useful clinical tool to evaluate postural instability in patients with parkinsonism who could also presents with stooped posture, freezing (difficulty initiating gait), shuffling (short step length), and asymmetric arm swing with rest tremor.

Clinically-Guided Supplementary Testing of the Neurological Syndrome in the Office Visit

A thorough clinical evaluation with focused history and examination guided by the chief complaint will often reveal the likely location of the lesion and its potential etiology. Supplementary testing is often useful in delineating the underlying diagnosis.

Imaging studies with computed tomography (CT) and magnetic resonance imaging (MRI) of the brain and the spinal cord are among the most useful tools to exclude, detect, or further characterize structural lesions. CT and MR angiograms are useful when evaluating vascular abnormalities such as stenosis, dissection, or cerebral arterial aneurysm.

Other commonly used tests include electroencephalogram (EEG) in patients with suspected seizures. Nerve conduction study and electromyography (EMG) studies are only used to evaluate neuromuscular processes. Autonomic tests are utilized when there is concern regarding dysautonomia. Evoked potentials (EP) like the Visual EP are useful when there is suspicion of optic nerve or visual reduction demyelination. Cerebrospinal fluids (CSF) analysis is important to exclude inflammatory, infectious or neoplastic processes. Removal of a large volume of CSF with gait and cognitive assessment prior to and after the procedure is performed for assessment of possible communicating hydrocephalus. CSF levels of amyloid and tau are useful in supporting a diagnosis of Alzheimer's disease (characterized by decreased amyloid and elevated tau levels).

If these specialized tests are being considered, then it is appropriate to obtain a neurological consultation. Preliminary workup could be initiated prior to the patient being evaluated by the specialist. Laboratory tests including a glycosylated hemoglobin (HbA1c), coagulation profile, and lipid panel will be necessary in cases with suspected cerebrovascular condition to stratify vascular risk factors. For patients with memory difficulties and peripheral neuropathy, screening for potentially treatable metabolic and nutritional causes such as checking a metabolic panel, vitamin B12, folate, methylmalonic acid and thyroid-stimulating hormone (TSH) is key. In cases of suspected myopathic processes, creatinine kinase and aldolase levels should be considered in addition to TSH.

The decision to obtain specific tests is guided by clinical information. Neurological examination is conducted to localize the likely site of the lesion, and in conjunction with the presenting history helps the clinician to generate differential diagnoses. The tests are then performed to identify for the most likely diagnoses.

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Chapter 2

Neuropsychological Evaluation

Aaron Bonner-Jackson

Clinical Pearls

- Neuropsychological testing can be useful in older adults to assist in differentiating neurodegenerative diseases (e.g., Alzheimer’s disease) from potentially reversible or treatable conditions (e.g., depression, sleep disturbance) or normal aging.
- Memory impairment is the cardinal symptom of Alzheimer’s disease and is characterized by poor learning of new information, rapid forgetting, and minimal benefit from recognition cues/reminders (i.e., amnesic memory profile).
- Neuropsychological evaluation is not recommended for patients in the moderate to severe dementia range, as they are not likely able to adequately participate in testing.

Introduction

Neuropsychology is the study of brain-behavior relationships. Neuropsychological evaluations utilize specialized cognitive assessment techniques to assist in a variety of clinical and research activities, including differential diagnosis, lesion localization, disability determination, competency evaluation, and assessment of cognitive change following a neurological event (e.g., stroke, traumatic brain injury) [1, 2]. A neuropsychologist is a doctoral-level clinical psychologist who has received specialized training in neurology, neuroanatomy, neuroscience, assessment, and treatment of psychological disorders.

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The structure of the neuropsychological evaluation varies somewhat based on the clinical setting but typically includes several standard elements. In addition to a review of previous medical records, the clinical interview is conducted to establish the patient's cognitive complaints and to collect additional relevant historical information (e.g., medical issues, academic history, occupation, psychiatric history). The neuropsychologist may gather information from collateral sources (spouse, family member, close friend) who may provide additional observations and insights into the patient's cognitive and behavioral changes. These observations become particularly valuable in assessing patients with neurological disorders, such as Alzheimer's disease, as these patients typically have limited insight into their own cognitive limitations and behavioral disturbances.

The neuropsychological testing battery varies as a function of patient population and clinical need, but most batteries encompass some combination of the measures listed in Table 2.1. Neuropsychological tests are administered and scored in a standardized manner. Most tests are "paper and pencil" tests, while some are administered via computer or tablet, and they measure examinees' ability to learn and recall information, solve problems, and think quickly, among other skills. Exams generally take place in a one-on-one setting and ideally should occur in a quiet, distraction-free environment (e.g., private office), although this is not always possible (e.g., inpatient hospital unit). After completion of the neuropsychology battery, tests are scored and the patient's scores are interpreted relative to normative data that are demographically corrected to account for the patient's age and education level, among other factors. In most cases, a cognitive profile can be generated that characterizes the patient's relative strengths and weaknesses. The neuropsychologist then interprets this profile in the context of other factors (e.g., medical history, neurological symptoms, mood, imaging findings) to hypothesize which neural systems may be most affected, what factors are most likely contributing to these findings, and what disorders should be considered in the differential diagnosis [3, 4]. Neuropsychological evaluations also typically provide recommendations for the patient regarding additional treatments, work-up, or compensatory techniques that may be utilized to address their cognitive issues.

Table 2.1 Domains assessed in typical neuropsychological evaluation

Domain	Typical measures used
Memory	Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Wechsler Memory Scale-IV
Language	Boston Naming Test, phonemic verbal fluency, semantic verbal fluency, sentence repetition
Attention	WAIS-IV Digit Span, Paced Auditory Serial Addition Test
Speed of processing	Trail making test (part A), WAIS-IV Coding, Symbol-Digit Modalities Test (SDMT)
Visuospatial	WAIS-IV block design, Rey-O complex figure test
Executive functioning	DKEFS Tower, WCST, trail making test (part B)
Motor function	Finger tapping test, grooved pegboard, grip strength
Mood/personality	Beck Depression Inventory, Beck Anxiety Inventory, Geriatric Depression Scale

WAIS-IV Wechsler Adult Intelligence Scale, 4th edition; *DKEFS* Delis-Kaplan Executive Function System; *WCST* Wisconsin Card Sorting Test

A repeat evaluation is often useful to more precisely determine whether the patient's cognitive deficits are progressive in nature and may be more sensitive than structural MRI at detecting disease progression [5].

Cognitive Changes Associated with Normal Aging

Among other changes, advancing age is associated with declines in aspects of cognitive functioning. Beginning in early adulthood, most individuals experience mild and gradual declines in certain cognitive functions, with the greatest age-related changes involving episodic memory, working memory, processing speed, and visuospatial skills [6]. Mild word finding difficulties, such as the “tip of the tongue” phenomenon, are common as individuals age. Some researchers have argued that declines in core cognitive abilities (e.g., speed of information processing, working memory capacity) result in reduced cognitive efficiency and can account for many of these changes [6]. Accompanying these cognitive changes are mild and gradual alterations of brain structure, including global loss of brain tissue, accumulation of white matter disease, and changes in neurotransmitter function [7]. These cognitive and brain changes are generally thought to accompany “normal aging” and are not considered to be pathological.

Of note, some cognitive skills remain relatively impervious to normal aging and can remain stable for most of one's lifetime. Such abilities include vocabulary, general fund of knowledge, and implicit memory.

Some of the cognitive domains commonly affected by normal aging are described below, followed by a description of how such cognitive abilities may be assessed using neuropsychological techniques.

Declarative Memory

Memory loss is a common complaint among older adults. In particular, older individuals frequently report difficulties with short-term memory, such as recalling a recently-learned name or why they entered a room. At the neural level, such changes are often attributed to inefficiencies in functioning of the frontal lobes, especially the prefrontal cortex, as abnormalities in this region are commonly reported in functional neuroimaging studies of memory function in older adults [8, 9].

Declarative (or episodic) memory can be tested in various ways, using different materials and different modalities (i.e., verbal/auditory, non-verbal/visual). Memory is often segmented into discrete processes (i.e., learning, recall, recognition), and careful neuropsychological examination allows each stage to be measured and analyzed separately. In the course of a neuropsychological examination, older adults may show signs of memory dysfunction in various ways including inefficient learning, such as reduced benefit from repeated presentations of materials. They also may demonstrate difficulty retrieving information, which manifests as reduced recall of infor-

mation following a delay period. Importantly, however, healthy older adults generally are able to retrieve previously-learned information when provided with recognition cues, suggesting that the information has been stored successfully.

Working Memory

Working memory refers to the ability to maintain and manipulate information for a brief period of time, usually a few seconds, and is theorized to encompass both verbal (phonological) and non-verbal (visuospatial) components. For example, mentally reordering a phone number into a numerical sequence would require verbal working memory. Older adults show a clear decline in working memory ability relative to younger individuals (see [10], for a review). One prevailing theory posits that older adults experience declines in working memory due to reductions in inhibitory control, which typically allows individuals to filter out irrelevant or interfering stimuli [11]. This results in increased cognitive inefficiency and inability to focus attention as effectively.

Working memory is measured in several ways throughout the neuropsychological evaluation, both directly and indirectly. Direct measures of working memory include tasks such as the digit sequencing task in which an individual hears a string of numbers and must mentally reorder them in a specified manner (e.g., numerical order). Other tasks, such as the Paced Auditory Serial Addition Test (PASAT), require the individual to quickly add pairs of auditory-presented numbers sequentially. For example, after hearing the first two numbers, the patient must sum them and state their answer verbally. After hearing the third number in the sequence, the patient must add it to the second number heard and again give the total. The test progresses in this fashion at a steady rate; most patients find it very challenging.

Working memory may be measured indirectly during the evaluation on tasks putatively measuring other cognitive abilities. For example, a test of non-verbal problem solving may require a significant working memory component, as the individual must maintain in working memory the rules of the task, previous moves made, and plans for future moves, among other information. Similarly, an individual may perform poorly on a word list memory task secondary to poor working memory if they cannot maintain words in their head long enough to learn them.

Processing Speed

Slowed processing speed is a commonly-reported phenomenon among older adults and is posited to account for many of the cognitive changes that are typically linked with aging [7, 12]. In particular, reduced speed of information processing is thought to diminish the amount of information available to an individual at any given time,

which limits their capacity for complex cognitive operations. It also renders individuals slower in completing tasks, thereby causing them to be more “inefficient”. Such slowing can have downstream effects on cognition, as slowed processing speed often limits capacity for new learning and may mimic a memory disorder. Therefore, careful interviewing and cognitive testing is crucial to parse various contributions to cognitive changes.

Information processing speed can be assessed in a variety of ways. A common neuropsychological instrument used for this purpose is the Trail Making Test, Part A (TMT-A), which requires individuals to draw lines connecting numbers that are scattered throughout the page. Numbers are to be connected in increasing numerical order (i.e., from 1 to 25), and the task is to be completed as quickly as possible. Scoring is based on time elapsed to complete the task, such that higher scores are achieved by faster task completion. Healthy older adults often can complete the measure with minimal errors but are typically slower than their younger counterparts.

Other measures can be used that require minimal fine motor function (i.e., writing/drawing) for individuals with a motor disturbance or similar limitation. The Symbol Digit Modalities Test (SDMT) is a substitution task that requires individuals to pair digits with certain geometric shapes based on a reference key. The oral version of this measure requires only verbal responses. Again, scoring is based on number of items completed within the time limit.

Additionally, many measures commonly administered during a neuropsychological evaluation have a timed or “speeded” component to them, although they may function primarily as measures of other cognitive skills. For example, the Block Design subtest of the Wechsler Adult Intelligence Scale-4th Edition (WAIS-IV) requires individuals to use blocks to construct designs of increasing complexity and is intended primarily as a measure of visuoconstruction ability. However, the measure also has a time limit, as well as bonus points for faster completion of designs, thereby assessing speed of processing.

Use of Neuropsychology in Assessment of Neurological Conditions

The above discussion highlights cognitive changes that commonly occur in the course of normal aging and the methods that can be used to assess these skills in a neuropsychological evaluation. Similarly, neuropsychological examination can be used to evaluate individuals with suspected neurological and neurodegenerative disorders. Results of neuropsychological evaluation can provide valuable information that may assist in differential diagnosis, staging of disease, response to treatment, disposition/care requirements, and/or assessment of recovery from an injury, among other data. Below are described two common neurological syndromes in the elderly for which neuropsychological evaluation may be sought.

Neurodegenerative Condition: Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia and becomes increasingly common with advancing age. For those over the age of 65, the risk doubles approximately every 5 years. As such, AD is often a diagnostic consideration when assessing older adults with concerns about memory loss or changes in functional status. Such individuals may be referred for neuropsychological evaluation to characterize their cognitive changes and provide a more formal assessment of their abilities in various domains. This evaluation also may serve as a baseline to assist in determining whether the individual's cognitive difficulties are progressive.

Among individuals with AD, *memory* is typically the domain that manifests the earliest changes, coinciding with early pathological changes found in the mesial temporal lobe, particularly the hippocampus. As described above, memory function can be assessed in a variety of ways, including evaluation of encoding, delayed recall, and recognition. Individuals with AD often show decrements in their ability to efficiently learn new information, and they often do not benefit significantly from repeated presentations of material. Following a delay period, they typically recall very little of the previously-presented information. Importantly, their performance does not improve significantly when they are provided with recognition cues, suggesting that the information has not been retained (i.e., rapid forgetting).

A second cognitive domain that is commonly affected relatively early in AD relates to language function, likely secondary to early temporal lobe pathology. Individuals in the early stages of AD, as well as their relatives, frequently report difficulty with verbal expression, including finding words in conversation and feeling as though a word is on the "tip of their tongue". They also have "empty speech," may use incorrect words (i.e., paraphasias), or talk around a word (i.e., circumlocution) due to their inability to retrieve the correct word. Neuropsychological evaluations often include measures of confrontation naming, such as the Boston Naming Test, which require individuals to name line drawings of objects that are presented to them visually. Verbal fluency measures, including phonemic and semantic fluency, are also typically provided during the testing and require individuals to rapidly generate words under certain conditions, either beginning with certain letters (phonemic fluency) or belonging to certain categories (semantic fluency). While performance of both tasks may be reduced in early AD, semantic fluency in particular tends to be impaired due to diminished semantic memory function.

Declines in executive functioning are also commonly observed relatively early in the course of AD. Executive functions encompass a range of higher-order cognitive skills, including problem solving, planning, multi-tasking, reasoning, and inhibitory control. Structures in the frontal lobes generally subservise executive abilities, although the performance of many executive tasks is thought to involve interconnected frontal-subcortical networks making them very sensitive to even more subtle changes. Tasks such as the Trail Making Test (Part B) are often administered and assess an individual's ability to rapidly switch between two mental sets—connecting numbers in numerical order and letters in alphabetical order. The Similarities

subtest of the WAIS-IV requires individuals to identify commonalities between two items or concepts and assesses verbal abstract reasoning. Measures such as the Tower subtest (from the Delis-Kaplan Executive Function System) or the Wisconsin Card Sorting Test (WCST) assess novel problem solving, hypothesis generation, and mental flexibility, among other skills. Individuals with AD are likely to perform poorly on many of these measures, although their degree of executive dysfunction is often reduced relative to changes in memory and language, at least initially.

Focal/Lateralized Condition: Left Hemisphere Stroke

Neuropsychological evaluations can be used to elucidate cognitive deficits in focal or lateralized neurological conditions. A common example involves neurocognitive changes that may occur following a large vessel stroke. Similar to AD, stroke increases in likelihood with age and represents the second leading cause of death worldwide [13]. Post-stroke dementia also occurs in up to one-third of patients, which suggests the necessity of thorough neuropsychological assessment to characterize cognitive changes and assist in treatment planning, including referral to other specialties (e.g., speech therapy). By way of example, below are outlined some of the common cognitive features associated with a left middle cerebral artery (MCA) stroke, as well as neuropsychological tools often utilized in assessment of patients with focal stroke syndromes.

As may be expected based on the anatomical location and vascular distribution, left MCA stroke is expected to produce weaknesses in language skills among individuals with left hemisphere language dominance. Depending on the specific distribution affected, patients may show impairments in specific language skills (e.g., repetition, comprehension, fluency). They also may show a more global aphasia syndrome, resulting in very limited verbal expression and comprehension.

Depending on the severity and extent of the patient's language deficits, the neuropsychological battery and test administration may be altered or abbreviated to accommodate their abilities. In general, however, a neuropsychological evaluation will often assess various aspects of language function (e.g., comprehension, repetition, fluency, naming) to characterize their deficits, potentially identify the presence of a specific aphasia syndrome, and provide a baseline for comparison purposes. Formal aphasia assessment batteries, such as the Boston Diagnostic Aphasia Examination (BDAE) or the Western Aphasia Battery (WAB), may be utilized for this purpose, although these measures tend to be fairly extensive and time-consuming, and neuropsychologists may choose to use a subset of these measures.

In addition to primary language deficits, memory for verbal materials (i.e., stories, words) also may be disproportionately affected relative to memory for comparable non-verbal materials (i.e., shapes, faces). For this reason, comparison of verbal vs. visual memory performance can be useful and may assist in generating recommendations for the patient. Such recommendations may suggest use of visual/non-

verbal cues (rather than verbal or written materials) as reminders, or using demonstration (rather than spoken directions) when teaching someone a new skill or activity.

Further, individuals with left hemisphere stroke often have fairly intact insight into their weaknesses and limitations, which may cause them significant frustration and depression. This is in comparison to those with right hemisphere stroke, which is more commonly associated with limited awareness of their cognitive changes or a neglect syndrome. As such, a thorough assessment of mood is a crucial aspect of the evaluation. This may be accomplished through careful history gathering, including reports from the patient and a collateral source (e.g., spouse, family member) regarding changes in mood. Self-report mood screening instruments, such as the Beck Depression Inventory-2nd Edition (BDI-2), are also commonly used and can be helpful in characterizing symptom severity.

Summary

Neuropsychological evaluation can be a valuable tool in the assessment of cognitive functioning among various groups, including patients with cognitive and/or neurological disorders, as well as healthy older adults. There are a wide variety of instruments and measures available that can be used flexibly to provide useful cognitive data in numerous settings. Careful assessment can yield information that assists in differential diagnosis, staging of disease, evaluation of treatment effects, or establishment of a cognitive baseline. Results of such examinations also can provide information regarding suitability of a patient to return to work or to live independently. Neuropsychological assessments may be considered as one component of a multidisciplinary neurological evaluation.

ICD-10 Codes

96118: Used to bill for professional (neuropsychologist) time, including face-to-face testing and data gathering, case conceptualization, report writing, and face-to-face feedback time.

96119: Used to bill for technician face-to-face testing time.

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Chapter 3

Mild Cognitive Impairment and Prodromal Alzheimer's Disease

Jeffrey Cummings and Kate Zhong

Clinical Pearls

- 50% of patients with mild cognitive impairment are in the prodromal phases of Alzheimer's disease.
- Patients with mild cognitive impairment progress to Alzheimer's disease dementia at a rate of approximately 15% per year.
- Patients with mild cognitive impairment may remain stable for many years or may recover to normal cognition.
- Brain health recommendations are appropriate for MCI patients. Guidance can be found at healthybrains.org.

Introduction

Mild cognitive impairment (MCI) is defined as a state of cognitive decline in which the patient has complaints of cognitive decline and on examination has impairment in one or more cognitive functions compared to their previous level of function. MCI patients have no or little functional impairment of activities of daily living (ADL) and do not meet criteria for dementia [1]. Episodic memory is the cognitive domain most commonly affected, involving recent or short-term memory such as recalling recent events in life or having trouble recalling lists of words (amnestic MCI). Other cognitive functions such as language, visuospatial function or

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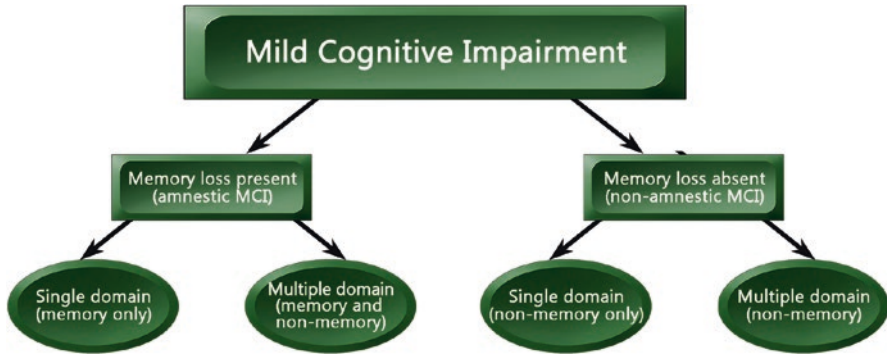


Fig. 3.1 Classification of forms of MCI

executive function may be affected in conjunction with memory (multi-domain amnesic MCI) or without memory function (non-amnesic MCI) [2] (Fig. 3.1).

MCI is a clinical concept and can be diagnosed without the assistance of quantitative mental status assessments. It is often operationalized for clinical trials and research purposes using specific neuropsychological tests of memory and other domains and using specific cutoffs to define abnormality (e.g., 1.0, 1.5 or 2 standard deviations below age- and education-matched controls) [3].

MCI is an etiologically heterogeneous and diagnostically non-specific clinical entity. In some cases it is the earliest form of clinically manifest Alzheimer’s disease (AD), in others it is the earliest form of another type of dementia (e.g., frontotemporal dementia [FTD], dementia with Lewy bodies [DLB], vascular dementia [VaD]). MCI can remain stable for many years and some patients exhibiting MCI can revert to normal cognition [4]. Identifying MCI is not equivalent to diagnosing AD; additional testing must be done to establish which patients with MCI are in the earliest phases of AD. Approximately 50% of amnesic MCI patients will progress to AD within the ensuing 5 years [5]. Thus, MCI represents a substantial risk state for AD. MCI with biomarker evidence of AD is labeled “prodromal AD” [6].

Prodromal Alzheimer’s Disease

Prodromal AD (pAD) is part of a continuum extending from biomarker positive preclinical AD, to prodromal AD, to AD dementia (Fig. 3.2) [6]. Positive amyloid imaging and reduced CSF amyloid are evident approximately 15 years prior to the onset of AD dementia. This long preclinical phase is followed by prodromal AD in which patients most commonly exhibit episodic memory impairment with no dementia and no/or little functional impairment in the presence of a positive biomarker such as amyloid imaging or the cerebrospinal fluid (CSF) signature of AD (comprised of reduced levels of amyloid protein ($A\beta_{1-42}$) and elevated levels of tau or phospho-tau (p-tau) protein [6]). Magnetic resonance imaging frequently shows



Fig. 3.2 Phases of AD

Table 3.1 Features of prodromal AD and AD dementia

Feature	Normal aging	AD at risk/preclinical AD	Prodromal AD	AD dementia
Cognition	Normal	Normal	Episodic memory loss	Multiple domain decline
Function	Normal	Normal	Normal	Impaired
CSF amyloid	Normal	Decreased	Decreased	Decreased
CSF tau-p-tau	Normal	Normal/increased	Increased	Increased
Amyloid imaging	Normal	Abnormal	Abnormal	Abnormal
FDG PET	Normal	Normal	Abnormal	Abnormal
MRI	Normal	Normal	Atrophy	Atrophy

hippocampal atrophy in patients with MCI and fluorodeoxyglucose positron emission tomography (FDG PET) may show reduced metabolism in the parietal lobes and the posterior cingulate gyrus [6]. MRI and FDG PET are progression biomarkers that provide evidence of state of the disease but are not diagnostically specific. Prodromal AD typically persists for approximately 5 years during which the patient has cognitive impairment but does not meet criteria for AD dementia.

Assessment of MCI

Assessment of MCI addresses medical causes of cognitive impairment, specifically vitamin B12 deficiency, vitamin D deficiency, and hypothyroidism. Delirium, depression, and adverse effects of medications, sleep apnea, excess use of alcohol, or substance abuse should be reviewed and excluded. In the absence of specific treatments for AD or other neurodegenerative disorders, the work-up may stop when these causes of MCI have been excluded and the patient is observed longitudinally to determine if AD or another dementia emerges. Appropriate treatment of the specific dementia (see Chap. 4) can then be implemented.

If the diagnosis of prodromal AD as a cause of MCI is required because the patient or the physician want this more specific information or the patient is to be entered into a research project or clinical trial, then appropriate investigations include amyloid imaging or a lumbar puncture to determine if the CSF profile of AD (low A β 1–42/high tau or p-tau) is present. Table 3.1 shows the features of the patient with prodromal AD and AD dementia.

Treatment of MCI

There is no specific treatment for MCI. Diagnosis of depression, delirium, sleep disturbance, alcohol or substance use, vitamin deficiency (B12, D), hypothyroidism, or other illness would lead to condition-specific treatment. Longitudinal follow-up is critical to determine if the patient is in the initial symptomatic stage of a neurodegenerative disorder that progresses to a more manifest, diagnosable, and treatable state. If the patient progresses to AD dementia, treatment with cholinesterase inhibitors and memantine may become appropriate (see Chap. 4).

Recommendations for a brain healthy lifestyle should be incorporated in patient discussions regardless of the cause of the MCI. Physical exercise, mental fitness, proper food and nutrition (e.g., a Mediterranean diet), social connectedness, stress reduction, sleep hygiene, and attention to dementia risk factors such as hypertension and hypercholesterolemia may slow the progression from MCI to AD or other neurodegenerative disease [7, 8]. A useful website is healthybrains.org.

ICD-10 Codes for MCI

Mild cognitive impairment G31.84.

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Chapter 4

Alzheimer's Disease

Charles Bernick

Clinical Pearls:

- The absence of memory symptoms early in the symptomatic course should cast doubt on the diagnosis of AD.
- Hallucinations occurring early in the clinical course should raise the possibility of an alternative diagnosis such as Lewy Body Disease (see Chap. 8) or presence of an intercurrent illness or drug effect.
- PET amyloid imaging has been correlated with plaque burden post-mortem. Thus, a negative PET amyloid study is inconsistent with a clinical diagnosis of AD dementia.
- Atrophy on MRI scan is not specific for AD; hippocampal volume loss can be seen in hippocampal sclerosis and other neurodegenerative diseases.
- Most individuals with dementia will have Alzheimer's disease, either by itself or with other brain pathologies; be alert to the presence of those other conditions.
- Regarding diagnosis, go low tech—most of the focus should be on obtaining a thorough history from an informant and probing for features that are not typical of Alzheimer's (early hallucinations, REM sleep behavior, early physical symptoms such as incontinence, gait or balance problems).
- Regarding treatment, subtract before you add—before adding an agent for AD, be sure to eliminate any drugs that may have an anti-cognitive effect if possible.

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia among older individuals. While AD is now recognized to be a disease process with a long prodromal phase (see Chap. 3), this section will focus on AD dementia, the point most likely to present to the physician and the phase of illness which demands the most resources from caregivers and the medical system.

Though the absolute percentage of the population with AD is hard to ascertain, several epidemiological characteristics are worth considering when evaluating the dementia patient [1]:

- Among individuals with dementia, AD pathology (either solely or in combination with other pathologies) is present in up to 80% of cases.
- Incidence and prevalence of AD roughly doubles every 5 years after the age of 65; the frequency of the disease at or below 65 years old is low, 1–2%, but in some estimates, reaches close to 50% of individuals over the age of 85.
- Genetics has a significant role in determining risk of AD [2]:
- There is an increased risk of AD among first degree relatives of cases.
- Young onset forms of familial AD that present in the third through sixth decade have been linked with mutations in three genes: the Amyloid Precursor Protein (Chromosome 21), presenilin 1 (chromosome 14) and presenilin 2 (chromosome 1).
- Apolipoprotein (ApoE) polymorphism E4 is associated with an increased risk of AD. Individuals homozygous for E4 carry a tenfold increased risk of AD, with some estimates suggesting a 90% risk by their mid to late 70s, whereas those heterozygous for E4 are at four times the risk of non-carriers and are at 50% risk of developing AD by their mid to late 70s.

Clinical Manifestations

The symptomatic hallmark of AD is impaired memory function—initially involving recall of new information such as conversations, names, object locations—with remote memories relatively preserved [3]. However, over time, even distant memories become effected, either forgotten or jumbled.

Higher levels of cognitive processing (“executive” functions) are also affected relatively early in AD. Difficulty with tasks involving planning, reasoning, decision making or judgment become apparent. Impairment in these spheres may manifest by problems performing more complex tasks such as home repairs or other projects around the house, coordinating large family meals, or making prudent financial decisions.

Eventually, the entire gamut of learned processes recede. Concerns about word finding may occur early in AD but generally language abilities are preserved. As the disease progresses, patients may become more obviously aphasic, either producing language without much meaning or more commonly, loss of fluency and inability to converse. Impaired visuospatial abilities lead to getting lost in familiar places, including, when advanced, one's home. In moderate to severe stages of AD, the development of apraxia results in increased dependence on others as hygiene and

grooming (brushing teeth for example), and eventually feeding and toileting are affected. Patients also may lose the ability to recognize objects (agnosia).

Often behavioral changes are present as an early feature of AD. Apathy and loss of initiative/motivation are common and not infrequently mistaken as depression. Depressive symptoms can occur in AD as well, with estimates suggesting occurrence in up to 30–50% during the course of disease [4]. Differentiating apathy from depression is assisted by the absence of other depressive symptoms such as anhedonia, sad mood, or vegetative symptoms in apathetic patients. And even when depression is present, it is often influenced by environmental manipulation with major depression being rare in AD.

Irritability or poor impulse control can be observed early in the disease process in some individuals. Caregivers may report that the patient’s premorbid personality has been accentuated, though some individuals seem to have a distinct change in their patience level. Unfortunately, some behavioral problems are amplified by the caregiver’s approach to the patient.

As AD progresses, other behavioral symptoms may emerge including delusions and hallucinations. The former may take the form as delusions of theft, infidelity, misidentification of family members, or that their house is not their home. Hallucinations are less common and usually visual.

There are certain symptoms or clinical signs that are not typical of AD and include the presence of: gait disturbance, motor impairment, incontinence or seizures early in the course (though all of these symptoms can occur later in the disease). Table 4.1 provides clinical features that aid in diagnosis.

While episodic memory loss is considered the hallmark symptom of AD, several non-amnestic presentations have been recognized and discussed separately (see Chap. 5). These have as the primary clinical features:

- Progressive language impairment (logopenic aphasia).
- Progressive impairment of visual processing (posterior cortical atrophy).
- Dysexecutive and/or behavioral impairment (“frontal” AD).

Table 4.1 Diagnostic features

Typical of AD
Older age
Memory impairment prominent
Gradually progressive
Neurological signs absent
Apathy, withdrawal
Not typical of AD
Acute/subacute onset
Younger age
Neurological signs present
Presence early in the course:
Gait disturbance
Incontinence
Seizures
Hallucinations

Diagnosis

Specific criterion for the diagnosis of AD have been developed by the International Work Group (IWG; see Chap. 3) and the National Institute of Aging and the Alzheimer's Association (NIA/AA) (Table 4.2). These criteria shares with others in the literature the requirement for the presence of dementia, a gradually progressive course and absence of other specific causes for the dementia [5]. Using the NIA/AA criteria, the positive predictive value for the diagnosis of AD has generally exceeded 80–85%. However, the specificity of the diagnostic criteria tends to be lower, closer to 60% [6].

The diagnosis of AD dementia can be made with the basic elements of a good clinical history of illness, neurological examination and laboratory/imaging testing (Fig. 4.1).

Possible AD dementia (Table 4.3) is diagnosed when patients with features of AD have atypical or mixed presentations.

Examination

Evaluation of the dementia patient begins with a thorough history, but generally not from the patient. Though some AD patients do have insight into their illness, it is imperative to obtain information from a reliable collateral source. Obtaining a history of short term memory impairment of gradual onset and progression with other cognitive functions declining, in the absence of any marked physical changes early, is a necessary start to the diagnosis.

The neurological examination is focused on both confirming the reported cognitive changes via mental status testing and surveillance for any neurological signs that may point to an alternative diagnosis. Several standardized cognitive screening tests are available with the Mini Mental Status Examination (MMSE) and Montreal Cognitive Assessment (MoCA) being two of the most commonly used. While both are easily administered, their limitations are worth keeping in mind. The MMSE lacks any assessment of “executive” function, is heavily weighted toward orientation, has a ceiling effect and can be influenced by education, ethnicity, and other factors. Alternatively, the MoCA is useful in detecting milder degrees of impairment and does include tests that reflect executive functioning [8].

Until the later stages of the disease, AD progresses in the absence of any marked physical changes. Thus presence of focal neurological signs or extrapyramidal features directs one to an alternative diagnosis (e.g. vascular dementia or Lewy body disease).

Certain laboratory tests have become a routine part of the workup of AD with the purpose of eliminating other potentially reversible causes of dementia. The basic tests are listed in Fig. 4.1 with other studies that may be chosen as indicated by the clinical picture [9]. While most individuals with gradually progressive dementia will have a neurodegenerative or vascular etiology, a not insignificant proportion (about 15%) will have a comorbid condition that can be treated.

Table 4.2 NIA/AA diagnostic criteria for probable AD dementia (McKhann et al. [7])

1. Meets criteria for dementia described earlier in the text, and in addition, has the following characteristics:
A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days
B. Clear-cut history of worsening of cognition by report or observation; and
C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories
a. Amnesic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text
b. Nonamnesic presentations:
• Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present
• Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present
• Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present
D. The diagnosis of probable AD dementia <i>should not</i> be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; (b) core features of dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition
E. Probable AD dementia with increased level of certainty
F. Probable AD dementia with documented decline
In persons who meet the core clinical criteria for probable AD dementia, documented decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology
Probable AD dementia with documented decline is defined as follows: evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations
G. Probable AD dementia in a carrier of a causative AD genetic mutation
In persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, OR PSEN2), increases the certainty that the condition is caused by AD pathology. The workgroup noted that carriage of the $\epsilon 4$ allele of the apolipoprotein E gene was not sufficiently specific to be considered in this category
H. Probable AD dementia with evidence of the AD pathophysiological process
In persons who meet the core clinical criteria for probable AD dementia biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process

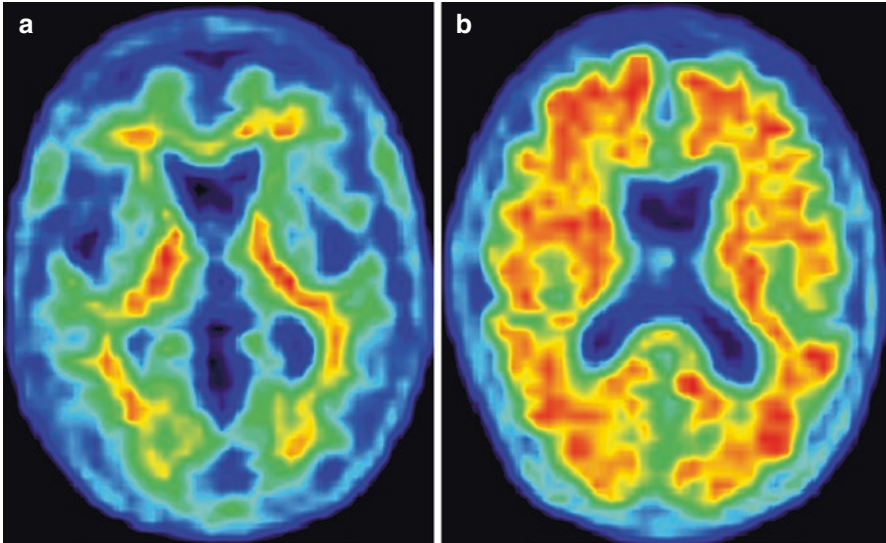


Fig. 4.1 Amyloid PET. (a) Normal; (b) abnormal with amyloid burden typical of AD

Table 4.3 NIA/AA diagnostic criteria for possible AD dementia (McKhann et al. [7])

A diagnosis of possible AD dementia should be made in either of the circumstances mentioned the following paragraphs

A. Atypical course

Atypical course meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline, or

B. Etiologically mixed presentation

Etiologically mixed presentation meets all core clinical criteria for AD dementia but has evidence of (a) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of dementia with Lewy bodies other than the dementia itself; or (c) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition

C. Possible AD dementia with evidence of the AD pathophysiological process

This category is for persons who meet clinical criteria for a non-AD dementia but who have either biomarker evidence of AD pathophysiological process, or meet the neuropathological criteria for AD

The diagnostic role of neuroimaging is to rule out structural lesions that can cause dementia. Non-contrasted Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT) of the brain are often adequate for that purpose. Of the two methods, MRI imaging can better visualize posterior fossa lesions or small vascular lesions, as well as patterns of focal atrophy.

Several *in vivo* biomarkers of AD are available and primarily focused on recognition of earlier stages of AD. While it is unclear yet how the clinical application of these markers improves diagnosis of AD dementia, there may be several potential roles of these biomarkers in the setting of the demented patient. It is known from clinicopathological studies that older individuals with dementia often have multiple pathologies at autopsy that may include amyloid plaques and tau protein tangles indicative of AD, along with cerebrovascular disease, Lewy bodies and other aggregated proteins. Having tests indicative of AD may assist in differential diagnosis and inform therapeutic decisions. Biomarkers for AD fall into two categories: those that reflect β amyloid accumulation and those that denote neuronal degeneration. Markers of amyloid deposition include decreased levels of β amyloid in the cerebrospinal fluid (CSF) (presumably due to β amyloid aggregation into fibrillar plaques) and elevated uptake of tracers that bind to amyloid on Positron Emission Tomography (PET) (Fig. 4.1). Studies to date suggest a relatively close correlation between these two markers [10]. Moreover, PET amyloid imaging has been correlated with plaque burden post-mortem. Thus, a negative PET amyloid study is inconsistent with a clinical diagnosis of AD dementia.

Several biomarkers of neuronal damage complement the amyloid markers. Rise in CSF total tau or phosphorylated tau is considered a marker of cellular injury and when coupled with low CSF β amyloid provides a diagnostic signature of AD.

Synaptic dysfunction may be reflected through ^{18}F - fluorodeoxyglucose (FDG) PET imaging. In AD, lower FDG uptake (lower glucose metabolism) is characteristically seen in the temporoparietal regions with involvement of precuneus and posterior cingulate (Fig. 4.2).

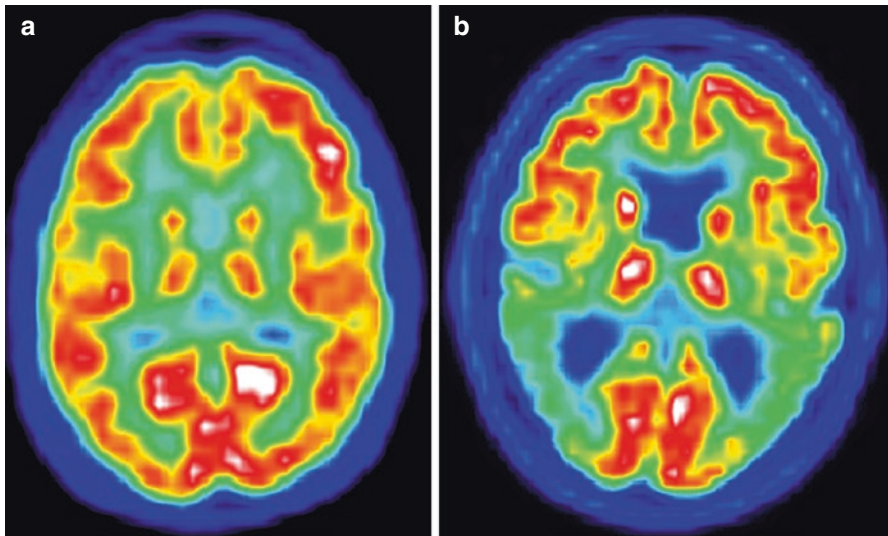


Fig. 4.2 FDG PET. (a) Normal; (b) abnormal with reduced temporo-parietal metabolism characteristic of AD

Regional atrophy on structural MRI imaging is also thought to indicate neurodegeneration. Volumes of medial temporal lobe structures, particularly hippocampus, are reduced in AD and can be measured by automated techniques.

While all of these biomarkers are commercially available, their cost effectiveness in AD diagnosis has yet to be demonstrated. The combination of volumetric MRI and PET markers provides useful findings supportive of a diagnosis of AD.

Though there are many possible causes of cognitive impairment in the elderly, several stand out to consider in the patient that presents with a history of chronic progressive cognitive decline. Cerebrovascular disease should be suspected in the patient with a history of vascular risk factors, stuttering/stepwise course, or neurological signs on examination such as focal findings, gait disturbance, hyperreflexia, or incontinence. To be confident of that diagnosis, one should see evidence of multiple infarcts or extensive white matter disease on structural imaging. Lewy body disease comes into the differential diagnosis with a history of visual hallucinations early in the course, fluctuating levels of alertness/daytime fatigue, rapid eye movement (REM) sleep behavioral disorder, and mild extrapyramidal signs on examination. Those with more acute changes in cognitive function or behavior should be vigorously evaluated for inappropriate medications or other systemic illnesses such as metabolic/infectious etiologies.

Treatment

The treatment of AD addresses cognitive and behavioral symptoms with symptomatic treatments. Although disease modifying strategies are under study, the current therapies have not been shown to slow progression of the disease.

The principal treatments for all severities of AD dementia are cholinesterase inhibitors (CEI). Three agents are currently approved in the United States, donepezil (Aricept™), rivastigmine (Exelon™) and galantamine (Razadyne™). Rivastigmine is available in patch form; donepezil and galantamine are given orally. These drugs putatively work by blocking acetylcholinesterase, the enzyme that degrades acetylcholine, thus increasing the cholinergic tone that is compromised as cholinergic neurons degenerate with disease progression.

The CEIs have repeatedly demonstrated a modest benefit on measures of cognitive function and Activities of Daily Living (ADLs). Notable improvement is seen in 20% of treated patients, with a larger proportion realizing a temporary lessening of symptomatic decline [11]. Given the less than dramatic response from CEIs, patients and caregivers need to be counseled on realistic expectations from these drugs. Yet it is worth remembering that delaying a symptomatic decline in ADLs may translate to being able to stay at more independent levels of home or residential care.

All CEIs are equally efficacious. On the other hand, the degree of cholinergic side effects may differ from agent to agent. The most common adverse effects are nausea and vomiting, bowel urgency or frank diarrhea (though other cholinergic effects can be seen such as vivid dreams, muscle cramps and bradycardia). The likelihood of these (or other side effects occurring) may be mitigated by slow titration of dose. If patients do not tolerate one CEI, it may be worth switching to at least one other.

Once an AD patient progresses to moderate to severe dementia, the addition of memantine (Namenda™) should be considered. An NMDA receptor antagonist, memantine is thought to reduce glutamnergic tone which has been shown to be increased in AD. This mechanism may improve signal transmission. In patients with moderate to severe AD, memantine slightly improves cognitive function and ADLs, and may have a favorable effect on behavior. Memantine has been shown to have efficacy either as monotherapy or in combination with a CEI. Dizziness has been noted as a possible side effect of memantine and it is available in immediate release and delayed release form, as well as in a combination capsule with donepezil (Namzaric™). Because the CEIs and memantine are thought to be only symptomatic drugs, it is worth discussing withdrawal of these medications if the patient has lost all ADLs and has no meaningful interaction with the family or caregivers.

Medical foods are a class of agents that are safe and address a metabolic defect but are not tested with the same rigor as drugs approved by the Food and Drug Administration (FDA). Axona™ is a medium chain triglyceride (caprylic triglyceride) proposed to address the metabolic defect of AD. Cerefolin™ is a B vitamin combination that treats hyperhomocysteinemia observed in some AD patients. Souvenaid™ is available in many countries and is composed of elements involved in supporting synaptic function.

There is an active industry promoting agents that are over the counter and said to improve cognitive health. Currently, there is no consistent evidence to recommend any of these agents. On the other hand, when feasible, lifestyle interventions that may have a pro-cognitive effect should be encouraged. Epidemiological studies have suggested that regular exercise, social engagement, good control of vascular risk factors and diets that include foods rich in antioxidants may have a positive effect on brain health in general. Helpful guidance can be found on healthybrains.org.

Behavioral disturbances are common in AD and can significantly complicate caregiving. Table 4.4 summarizes an initial approach to behavioral problems. While no therapeutic agents have a specific indication for behavioral disorders in AD, pharmacologic management of behavior is often based on how similar non-dementia diagnoses in psychiatry are treated. However, certain caveats need to be

Table 4.4 Non-pharmacological approach to behavioral symptoms

Exclude reversible causes of behavioral disturbance
Medications
Infections (e.g. UTIs, URIs) and other concurrent illnesses
Volume depletion
Discomfort (e.g. pain, constipation)
Identify and correct/adapt environmental conditions that may trigger behavior
If medications are used:
Target symptoms to be treated
Maintain lowest dose possible
Consider withdrawing if behavior remains under good control

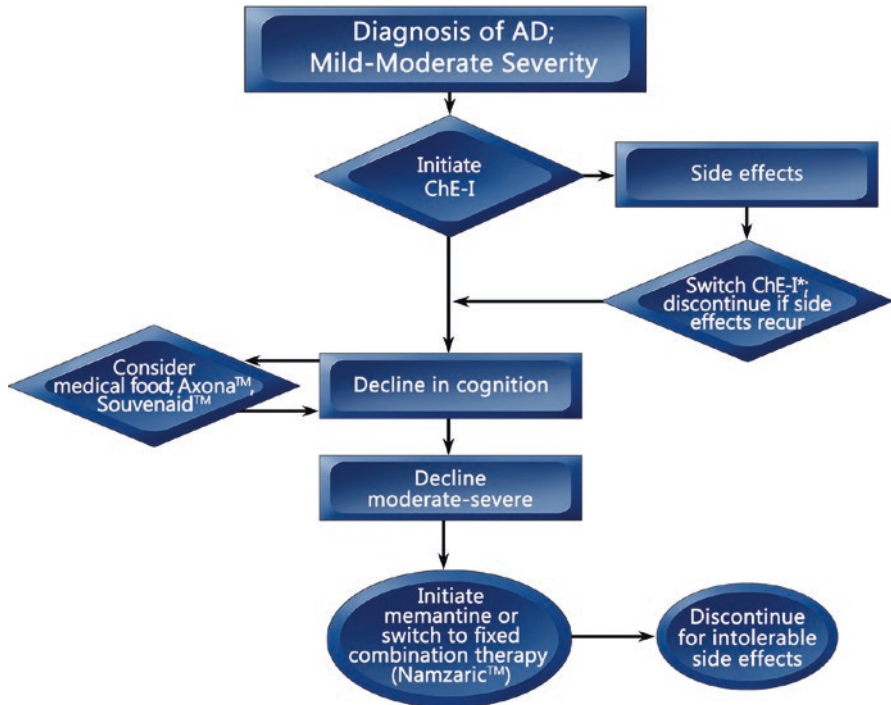


Fig. 4.3 Management of AD

considered in administering psychotropics to an elderly, dementia population including [12]:

- Antipsychotic medications carry a FDA “black box” warning of increased risk of stroke and death in older demented patients and should be considered if the psychosis is very disturbing for the patient or results in the patient being a danger to themselves or others.
- Benzodiazepines have been associated with increased confusion, sedation and falls in the elderly.

Figure 4.3 provides guides for pharmacotherapy of AD.

ICD-10 Codes

Alzheimer’s disease, unspecified	G30.9
Alzheimer’s disease with early onset	G30.0
Alzheimer’s disease with late onset	G30.1
Focal onset Alzheimer’s disease	G30.8

Disclosures Dr. Bernick is a speaker for Allergan.

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Chapter 5

Atypical Alzheimer's Disease, Mixed Dementia, and Amyloid Angiopathy

Jeffrey Cummings

Clinical Pearls

- Posterior cortical atrophy is most commonly caused by Alzheimer's disease but can be caused by Creutzfeldt-Jakob disease and other progressive neurological disorders
- Frontal Alzheimer's disease typically has a later onset than the behavioral variant of frontotemporal dementia
- Identification of amyloid angiopathy-related inflammation is important because some cases improve with steroid treatment

Atypical Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by a long preclinical period of silent amyloid accumulation, followed by a period of prodromal AD with mild cognitive impairment (MCI)/prodromal AD and a period of AD dementia featuring increasing cognitive and functional decline (see Chaps. 3 and 4) [1]. In most cases, the earliest signs evolving in the period of prodromal AD, include episodic memory abnormalities with impairment of new learning and short term recall. This pattern of memory loss reflects the early involvement of hippocampus and medial temporal structures with AD pathology. In some cases, however, AD involves other brain regions and consequently presents with a variant or atypical phenotype. The three recognized variants are: posterior cortical atrophy (PCA),

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logopenic aphasia, and frontal AD (fAD). In addition, AD may be associated with cerebrovascular disease or other comorbid conditions in “mixed dementia.” The criteria for these atypical and mixed forms of AD are presented here.

Posterior Cortical Atrophy

PCA is characterized by involvement of the posterior hemispheric structures producing Gerstmann syndrome (agraphia, acalculia, right-left disorientation, finger agnosia) or Balint’s syndrome (optic ataxia, ocular apraxia, and simultanagnosia). Agraphia refers to the inability to write correctly from a linguistic perspective despite otherwise normal language functions; acalculia is the inability to perform calculations and mathematical operations; right-left disorientation refers to an inability to distinguish left and right especially with complex multi-step commands; finger agnosia is the inability to properly identify named or touched fingers; optic ataxia is the inability to point accurately; ocular apraxia is the inability to follow environmental movements with the eyes normally, it often manifests as “sticky fixation”, the inability or impairment of disengaging from a visual target; simultanagnosia is the inability to perceive more than one object at a time in a complex visual environment. Table 5.1 presents the diagnostic criteria for PCA [2].

Table 5.1 Core features of the PCA clinico-radiological syndrome (from Crutch et al, 2017 [2])

Clinical, cognitive, and neuroimaging features are rank ordered in terms of (decreasing) frequency at first assessment

Clinical features:

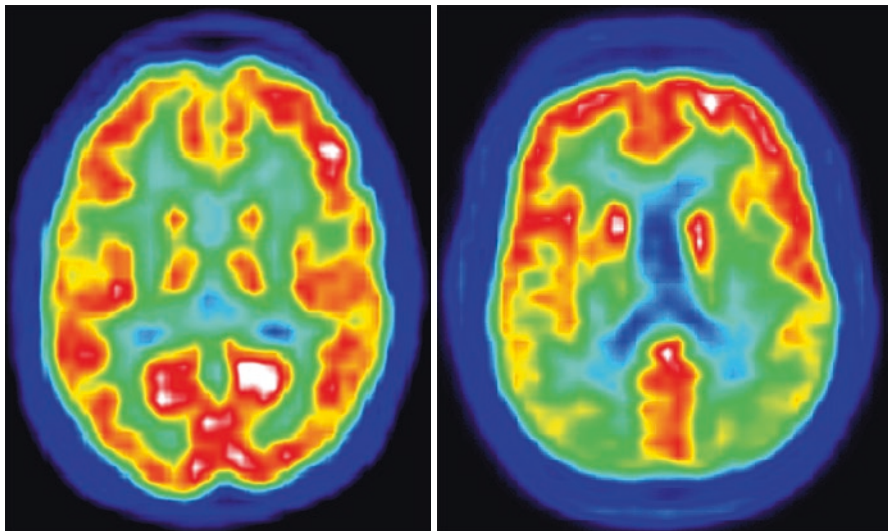
- Insidious onset
- Gradual progression
- Prominent early disturbance of visual \pm other posterior cognitive functions

Cognitive features:

- At least three of the following must be present as early or presenting features \pm evidence of their impact on activities of daily living:
 - Space perception
 - Simultanagnosia
 - Object perception deficit
 - Constructional dyspraxia
 - Environmental agnosia
 - Oculomotor apraxia
 - Dressing apraxia
 - Optic ataxia
 - Alexia
 - Left/right disorientation
 - Acalculia
 - Limb apraxia (not limb-kinetic)
 - Apperceptive prosopagnosia
 - Agraphia
 - Homonymous visual field defect
 - Finger agnosia

Table 5.1 (continued)

<ul style="list-style-type: none"> • All of the following must be evident: <ul style="list-style-type: none"> – Relatively spared anterograde memory function – Relatively spared speech and nonvisual language functions – Relatively spared executive functions – Relatively spared behavior and personality
Neuroimaging:
<ul style="list-style-type: none"> • Predominant occipito-parietal or occipito-temporal atrophy/hypometabolism/hypoperfusion on MRI/FDG-PET/SPECT
Exclusion criteria:
<ul style="list-style-type: none"> • Evidence of a brain tumor or other mass lesion sufficient to explain the symptoms • Evidence of significant vascular disease including focal stroke sufficient to explain the symptoms • Evidence of afferent visual cause (e.g., optic nerve, chiasm, or tract) • Evidence of other identifiable causes for cognitive impairment (e.g., renal failure)

**Fig. 5.1** FDG PET of patient with posterior cortical atrophy (PCA) (*Right*) compared to normal (*Left*)

PCA has a profound effect on activities of daily living (ADL). They have trouble reaching for eating utensils, cannot dress, and may have difficulty orienting toward chairs or couches. On examination, drawing and copying are markedly impaired.

PCA is most often caused by AD but the syndrome has also been produced by Creutzfeldt- Jakob disease, corticobasal degeneration, Lewy body dementia, and vascular dementia. A differential diagnostic process should be entertained when considering the causes of PCA [2].

If the assessment (like that outlined in Chap. 4) suggests that AD is the cause of the PCA, then treatment with cholinesterase inhibitors and memantine should be considered.

Fluorodeoxyglucose (FDG) positron emission tomography (PET) shows marked bilateral parietal hypometabolism (Fig. 5.1).

Table 5.2 Diagnostic criteria for logopenic variant of primary progressive aphasia (PPA) (from Gorno-Tempini et al. [3])

I. Clinical diagnosis of logopenic PPA
<ul style="list-style-type: none"> • Both of the following core features must be present: <ul style="list-style-type: none"> – Impaired single-word retrieval in spontaneous speech and naming – Impaired repetition of sentences and phrases • At least 3 of the following other features must be present: <ul style="list-style-type: none"> – Speech (phonologic) errors in spontaneous speech and naming – Spared single-word comprehension and object knowledge – Spared motor speech – Absence of frank agrammatism
II. Imaging-supported logopenic variant diagnosis
Both criteria must be present:
1. Clinical diagnosis of logopenic variant PPA
2. Imaging must show at least one of the following results: <ul style="list-style-type: none"> (a) Predominant left posterior perisylvian or parietal atrophy on MRI (b) Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on single photon omission computed tomography (SPECT) or fluorodeoxyglucose positron emission tomography (FDG PET)
III. Logopenic variant PPA with definite pathology
Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
1. Clinical diagnosis of logopenic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. AD, FTLT-tau, FTLT-TDP, other)
3. Presence of a known pathogenic mutation

Logopenic Aphasia

Patients with neurodegenerative disease may present with primary progressive aphasia (PPA) (see Chap. 9). The three recognized varieties of PPA are: progressive nonfluent aphasia (PNA), semantic dementia (SD), and logopenic aphasia. PNA and SD are variants of FTD. PNA is characterized by slow, sparse agrammatic speech, while semantic dementia features visual agnosia (inability to recognize objects visually although they can be recognized by touch) and semantic aphasia (fluent spontaneous output with reduced comprehension and repetition of language, paraphasic errors, and anomia).

Logopenic aphasia is usually caused by AD and has the following clinical features: relatively sparse speech, anomia, intact grammar [3]. Table 5.2 presents the diagnostic criteria for logopenic aphasia.

If precise diagnosis is required, amyloid imaging can be used to clarify the etiology of PPA. Most (approximately 70–90%) of patients with logopenic aphasia have positive amyloid imaging consistent with AD; most patients with PNA and SD have negative amyloid imaging consistent with a non-AD cause of the aphasia syndrome. PNA is usually indicative of an underlying tauopathy type of FTD, and tau imaging, if available, would be expected to be positive. Ten to 30% of logopenic aphasia patients have underlying FTD; similarly, 10–20% of PNA or SD patients will have positive amyloid imaging consistent with a diagnosis of underlying AD.

Table 5.3 IWG-2 criteria for atypical AD (frontal variant, AD) [7]

A.	Presence of early, predominant, and progressive behavioral changes including association of primary apathy or behavioral disinhibition, or predominant executive dysfunction on cognitive testing
B.	In-vivo evidence of Alzheimer's pathology (one of the following) <ul style="list-style-type: none"> • Decreased Aβ1-42 together with increased T-tau or P-tau in CSF • Increased tracer retention on amyloid PET • Alzheimer's disease autosomal dominant mutation present (in PSEN1, PSEN2, or APP)
Exclusion criteria ^a	
<i>History</i>	
<ul style="list-style-type: none"> • Sudden onset • Early and prevalent episodic memory disorders 	
<i>Other medical conditions severe enough to account for related symptoms</i>	
<ul style="list-style-type: none"> • Major depression • Cerebrovascular disease • Toxic, inflammatory, or metabolic disorders 	

^aAdditional investigations, such as blood tests and brain MRI, are needed to exclude other causes of cognitive disorders or dementia, or concomitant pathologies (vascular lesions)

Once the diagnosis of AD is made in a patient with logopenic aphasia, treatment appropriate for AD including cholinesterase inhibitors and memantine can be considered.

Frontal Alzheimer's Disease

Patients presenting with disinhibited, socially inappropriate behavior most commonly have the behavioral variant of FTD. However, some patients with AD may present with this syndrome. They tend to be older than the typical FTD patient and may have more severe memory impairment [4]. They are also likely to have behaviors such as agitation [5]. Table 5.3 presents the clinical features of fAD [6]. At autopsy, fAD patients have a disproportionately high burden of neurofibrillary tangles in the frontal lobes [4, 5].

When AD is recognized to be the cause of the frontal syndrome, treatment with AD medications can be considered including cholinesterase inhibitors and memantine.

Mixed Dementia and Alzheimer's Disease with Cerebrovascular

AD patients are elderly and comorbid medical and brain diseases are common [8]. Cerebrovascular disease (CVD) is especially common in AD and may result from small vessel disease associated with diabetes and hypertension, large vessel occlusion from emboli (e.g. with atrial fibrillation) or atherosclerosis, or amyloid angiopathy stemming from amyloid deposition the blood vessels of the brain (see Chap. 7). It may be difficult to distinguish mixed CVD-AD from VaD when a history of

strokes or neuroimaging evidence of multiple strokes is present. Evidence supporting the concomitant presence of AD in a patient with CVD includes:

- Insidious onset
- Gradual progression between episodes of acute stroke-related decline
- Family history of AD
- Apolipoprotein E epsilon-4 (ApoE-4) genotype
- Marked hippocampal atrophy on magnetic resonance imaging (MRI)
- Symmetric bilateral parietal and posterior cingulate hypometabolism (characteristic of AD) along with multifocal regional hypometabolism (characteristic of CVD) on FDG PET
- Positive amyloid imaging
- Cerebrospinal fluid (CSF) signature of AD (low amyloid-beta protein and elevated tau or phospho-tau protein)

In addition to mixed AD-CVD, AD can co-occur with any other disorder occurring in the elderly and the practitioner must be vigilant for possible concomitant disease that may be amplifying cognitive decline.

At autopsy, non-AD pathology is frequently found in patients who also meet pathology criteria for AD. This may include CVD, Lewy body pathology, amyloid angiopathy, and TDP-43 [9].

Amyloid Angiopathy

Congophilic amyloid angiopathy (CAA) refers to the deposition of amyloid in cerebral blood vessel; the term is based on the birefringent staining of the amyloid as seen with Congo red staining of the vascular depositions. The amyloid deposited in blood vessels is typically the 40 amino acid length; plaques of AD are comprised primarily of the 42 amino acid length variety of amyloid. CAA occurs in AD and also occurs in the absence of AD where it constitutes an independent cause of cerebrovascular disease.

CAA often announces itself in the form of multiple lobar hemorrhages. These hemorrhages differ from hypertensive hemorrhages that typically occur in the basal ganglia, brain stem, thalamus, and cerebellum. The hemorrhages of CAA occur more peripherally in parietal, temporal, occipital, or frontal lobes. CAA is also a major cause of microhemorrhages detected with gradient echo (GRE) sequences of magnetic resonance imaging (MRI). CAA should be suspected in any older individual with one or more lobar hemorrhages in the absence of other causes of hemorrhage. There is no specific treatment for CAA and the prognosis when identified is for more hemorrhages to occur over time with accumulating deficits. The presence of CAA and microhemorrhages is recognized as a risk factor for amyloid-related imaging abnormalities (ARIA) of the hemorrhagic (ARIA-H) and effusion (ARIA-E) type associated with some experimental passive immunotherapies for AD [10]. Table 5.4 provides the pathologic and clinical criteria for CAA [11].

A unique and potentially treatable form of CAA is amyloid-angiopathy-related inflammation. The diagnosis is based on recognition in individuals over age 40 of headache, decrease in consciousness, focal seizures or focal neurological signs; MRI with unifocal or multifocal white matter lesions; cerebral hemorrhage (macrobleed or microbleed) or cortical superficial siderosis; in the absence of neoplastic, infectious or other causes of these lesions [12]. Most individuals studied have been found to be ApoE-4 gene carriers. Table 5.5 provides clinical and radiologic criteria for probable and possible amyloid-angiopathy-related inflammation.

Table 5.4 Diagnostic criteria for amyloid angiopathy related hemorrhage (Knudsen et al. [11])

1. Definite CAA
Full postmortem examination demonstrating:
<ul style="list-style-type: none"> • Lobar, cortical, or corticosubcortical hemorrhage • Severe CAA with vasculopathy • Absence of other diagnostic lesion
2. Probable CAA with supporting pathology
Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating:
<ul style="list-style-type: none"> • Lobar, cortical, or corticosubcortical hemorrhage • Some degree of CAA in specimen • Absence of other diagnostic lesion
3. Probable CAA
Clinical data and MRI or CT demonstrating multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed)
<ul style="list-style-type: none"> • Age 55 years or more • Absence of other cause of hemorrhage
4. Possible CAA
Clinical data and MRI or CT demonstrating single lobar, cortical, or corticosubcortical hemorrhage
<ul style="list-style-type: none"> • Age 55 years or more • Absence of other cause of hemorrhage

Table 5.5 Diagnostic criteria for amyloid angiopathy-related inflammation (Auriel et al. [12])

Probable CAA-ri
<ul style="list-style-type: none"> • Age \geq 40 year • Presence of \geq1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute intracerebral hemorrhage (ICH) • MRI shows unifocal or multifocal white matter hyperintensities (corticosubcortical or deep) that are asymmetric and extend to the immediately subcortical white matter; the asymmetry is not due to past ICH • Presence of \geq1 of the following corticosubcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis • Absence of neoplastic, infectious, or other cause

(continued)

Table 5.5 (continued)

Possible CAA-ri
<ul style="list-style-type: none"> • Age \geq 40 year
<ul style="list-style-type: none"> • Presence of \geq1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH
<ul style="list-style-type: none"> • MRI shows white matter hyperintensities that extend to the immediately subcortical white matter
<ul style="list-style-type: none"> • Presence of \geq1 of the following corticosubcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis
<ul style="list-style-type: none"> • Absence of neoplastic, infectious, or other cause

Abbreviations: *CAA-ri* cerebral amyloid angiopathy–related inflammation, *ICH* intracerebral hemorrhage, *MRI* magnetic resonance imaging

A vital reason for identifying amyloid-angiopathy-related inflammation is that this condition has treatable aspects. Patients who fulfill the diagnostic criteria should be considered for treatment with a short course of high dose steroids or cyclophosphamide [13]. Reversal of symptoms is often dramatic with improvements in consciousness and gait.

ICD-10 Codes

Alzheimer's disease with late onset	G30.1
Alzheimer's disease with early onset	G30.0
Alzheimer's disease unspecified	G30.9
Focal onset Alzheimer's disease	G30.8
Mixed dementia: use AD	G30.0 or 630.1
Vascular dementia	F01
– Without behavioral disturbance	F01.50
– With behavioral disturbance	F01.51
Amyloid angiopathy	168.0

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Chapter 6

Acute Ischemic Stroke

Irene L. Katzan

Clinical Pearls

- Goals of management in the hyperacute and acute period are to (a) optimize cerebral perfusion and (b) minimize neuronal injury.
- Speed is critical in the evaluation and management of patients with acute ischemic stroke.
- The longer the time since the patient was last known well, the more critical becomes advanced imaging assessment of brain tissue with CT perfusion, MRI and MR perfusion to determine the risk and benefit of recanalization therapies.
- The main goals of the acute inpatient stay are to: (a) prevent neurological worsening; (b) prevent medical complications; (c) Optimize recovery, which entails initiation of physical, occupational, and speech therapies and discharge planning; (d) Initiate strategies to prevent recurrent stroke.

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Introduction

Stroke poses a tremendous health burden. Each year, approximately 795,000 people experience a new or recurrent stroke. On average, someone dies of a stroke every 4 min [1]. Although stroke is a leading cause of death, most stroke patients survive, and, as a result, stroke is a leading cause of long-term disability in adults in the United States. Of stroke patients that survive 5 years, one-third are disabled, and 1 in 7 are in permanent institutional care [2]. According to projections, an additional 4 million people will have had a stroke by 2030 due to the aging of the population and shift in population demographics. This represents a 21.9% increase in prevalence from 2013.

The acute management of stroke can have a significant impact on overall outcomes. Data have shown that administration of intravenous recombinant tissue plasminogen activator (IV rtPA) significantly increases the chance of patients being left with minimal to no disability [3]. Endovascular therapy of patients with large vessel occlusion has been shown to improve outcomes [4]. Importantly, the management of patients in stroke units, which largely entails the systematic following of general management principles for stroke, has consistently been shown to reduce mortality and improve functional outcomes [5]. A systematic approach to care is applicable to almost all acute stroke patients and has a larger overall impact on outcomes after stroke than does performing hyperacute intervention in isolation, for which only a minority of stroke patients currently are eligible. This chapter reviews the approach to management of patients with acute ischemic stroke.

Although stroke patients enter the treatment process from a number of different venues, they generally come either directly to the emergency department (ED) from home through emergency medical services (EMS) or private transport or are transferred in from other hospitals. This initiates the treatment process, which can be broken into two distinct phases: hyperacute stroke evaluation and inpatient management.

Hyperacute Stroke Evaluation and Management

Hospital Arrival—Immediate Considerations

The initial evaluation of a potential stroke patient should focus on immediate evaluation of the circulation, airway and breathing [6]. Oxygen saturations should be maintained at 94% or above. Supplemental oxygen is not recommended unless oxygen saturations fall below this threshold. It is important to avoid hypotension in the setting of acute ischemia. Blood pressure (BP) medications should not be administered unless systolic blood pressure (SBP) is over 220 mmHg or diastolic blood pressure (DBP) is higher than 120 mmHg, *except* for patients who are potential candidates for reperfusion therapy (IV rtPA or endovascular recanalization). *If acute intervention is being considered, these thresholds should be reduced to SBP \leq 185 mmHg and DBP \leq 110 mmHg* (see section “Acute Intervention 0–3 h”). *Serum glucose should be checked on arrival, and hypoglycemia or hyperglycemia above 200 mg/dL should*

be corrected. Hypoglycemia can result in symptoms that mimic an acute stroke. Hyperglycemia has been associated with worse outcomes. Patients should be placed on continuous telemetry for at least the first 24 h of admission [7].

Clinical Manifestations (History and Physical Examination)

Once vital signs have been assessed, a physical examination should be performed. This should include a neurological assessment as well as the *completion of the National Institutes of Health Stroke Scale (NIHSS) (Table 6.1). The time last known well should be determined.* This is critical as it is a central eligibility criterion for hyperacute interventions.

Table 6.1 National Institutes of Health Stroke Scale [8]

1A Level of consciousness
0—Alert
1—Drowsy
2—Obtunded
3—Coma/unresponsive
1B Orientation questions
0—Answers both correctly
1—Answers 1 correctly
2—Answers neither correctly
1C Response to commands
0—Performs both tasks correctly
1—Performs 1 task correctly
2—Performs neither correctly
2 Gaze
0—Normal horizontal movements
1—Partial gaze palsy
2—Complete gaze palsy
3 Visual fields
0—No visual field defect
1—Partial hemianopia
2—Complete hemianopia
3—Bilateral hemianopia
4 Facial movement
0—Normal
1—Minor facial weakness
2—Partial facial weakness
3—Complete unilateral palsy
5 Motor function (arm) a. Left; b. Right
0—No drift
1—Drift before 5 s

(continued)

Table 6.1 (continued)

2—Falls before 10 s
3—No effort against gravity
4—No movement
6 Motor function (leg) a. Left; b. Right
0—No drift
1—Drift before 5 s
2—Falls before 5 s
3—No effort against gravity
4—No movement
7 Limb ataxia
0—No ataxia
1—Ataxia in 1 limb
2—Ataxia in 2 limbs
8 Sensory
0—No sensory loss
1—Mild sensory loss
2—Severe sensory loss
9 Language
0—Normal
1—Mild aphasia
2—Severe aphasia
3—Mute or global aphasia
10 Articulation
0—Normal
1—Mild dysarthria
2—Severe dysarthria
11 Extinction or inattention
0—Absent
1—Mild (1 sensory modality lost)
2—Severe (2 modalities lost)

Diagnostic Approach (Diagnostic Care Path)

Laboratory

Blood should be drawn on arrival and laboratory work ordered right away. At a minimum, it should include prothrombin time (PT)/Partial thromboplastic time (PTT), complete blood count (CBC) with platelets, troponins, creatinine and a pregnancy test if the patient is a female <55 years old.

Imaging

Computed Tomography (CT) Head

A noncontrast head CT should be performed as soon as possible after arrival.

Computed Tomography Angiogram (CTA)

A CTA should be done to identify the presence of large-vessel occlusion if NIHSS score ≥ 6 or in those with fluctuating neurological symptoms even if NIHSS score < 6 . This identifies patients who are potential candidates for hyperacute endovascular therapy (see below) and is also helpful in the clinical management of patients' blood pressure and hemodynamic status within the first 24–48 h. Creatinine (determined by either lab draw or point-of-care testing if available) should be ≤ 1.4 mg/dL; however, the need for urgent imaging to identify large-vessel occlusion may outweigh the risks of kidney injury stemming from an elevated creatinine level.

Advanced Imaging

Advanced brain imaging with magnetic resonance imaging (MRI) or CT perfusion is often performed to select patients who are candidates for endovascular therapies. Advanced imaging allows better characterization of the volume of penumbra (potentially salvageable tissue) in relation to infarcted tissue; however, there is a lack of evidence on which parameters best characterize the tissue at risk.

Therapeutics (Treatment Care Path) (Fig. 6.1)

Acute Intervention 0–3 h

Intravenous rtPA is recommended for eligible patients within 3 h of time last known well (Class A, Level 1 recommendation [7]). Patients receiving IV rtPA have a 13% absolute increased chance of being left with minimal or no disability [3]. Within the time window for IV rtPA, the benefit of treatment declines as the time between onset to treatment increases, and speed of evaluation and initiation of management are critical [9]. IV rtPA should be administered within 60 min of the patient's arrival at the hospital; the sooner IV rtPA can be administered, the better the chance of improved outcome. Because of the delay inherent in performing the CTA and interpreting the images, processes for IV rtPA administration (e.g., mixing the IV rtPA, making a final determination of eligibility) should not wait until the CTA is completed.

Inclusion and exclusion criteria for IV rtPA administration, outlined in “Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke” [10] should be followed (Table 6.2). An important consideration is blood pressure control. It should be consistently less or equal to SBP 185 mmHg and DBP 110 mmHg. IV tPA should not be withheld until the laboratory values become available unless there is a clinical suspicion based on history or medication use that results may be abnormal. If platelets or INR are abnormal after initiation of IV rtPA, the infusion should be discontinued.

Patients receiving IV rtPA who have large-vessel occlusion (as demonstrated on CTA) with persistent deficits may also be candidates for endovascular therapy (see section “Endovascular Therapy”).

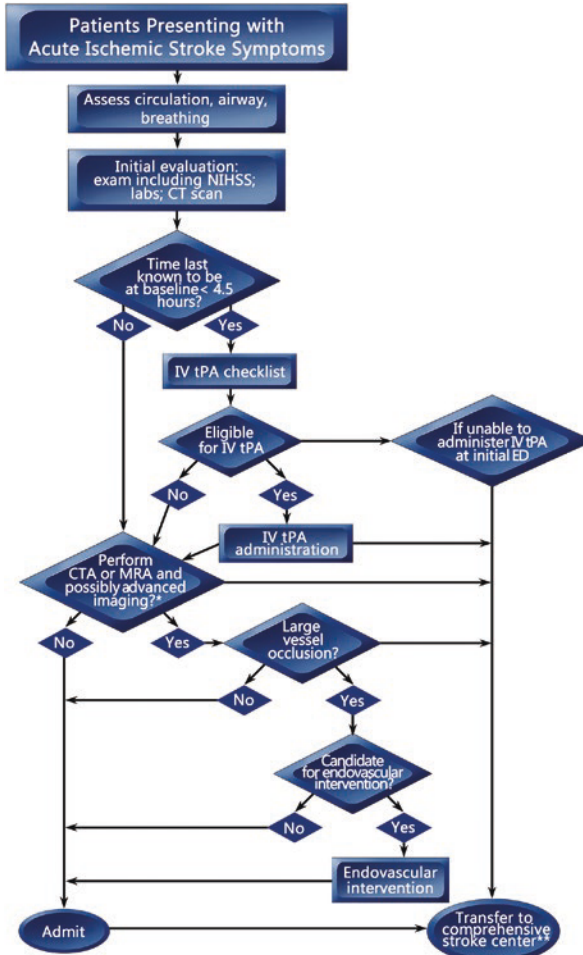


Fig. 6.1 Management of acute ischemic stroke patients during the hyperacute period. *NIHSS* National Institutes of Health Stroke Scale, *CT* computed tomography, *rtPA* recombinant tissue plasminogen activator, *CTA* computed tomography angiogram, *MRA* magnetic resonance angiogram. *Consider noninvasive intracranial vascular imaging if one of the following exists: $NIHSS \geq 6$, there are fluctuating symptoms, or it is hospital protocol. **At multiple time-points, may transfer to stroke center with capabilities to comprehensively manage ischemic stroke patients, including endovascular intervention

Acute Intervention 3–4.5 h

IV rtPA has been shown to improve outcomes if administered within the 3–4.5-h of last known to be at baseline [11] and is recommended for patients within this time window (Class I, Level B recommendation [10]). Not surprisingly, the benefit of rtPA administration within this later window is less than if given within 3 h. Eight patients

Table 6.2 Inclusion and exclusion characteristics of patients with ischemic stroke who could be treated with intravenous rtPA within 3 h from symptom onset (derived from Demaerschalk et al. [10])

<i>Inclusion criteria</i>
Ischemic stroke causing measurable neurological deficit symptoms
Onset of symptoms <3 h before treatment
Age \geq 18 years
<i>Exclusion criteria</i>
Significant head trauma in the previous 3 months
Stroke in the previous 3 months
Symptoms suggest subarachnoid hemorrhage
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial hemorrhage; intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mmHg or diastolic >110 mmHg)
Active internal bleeding
Acute bleeding diathesis, including but not limited to:
<ul style="list-style-type: none"> • Platelet count <100,000/mm³ • Heparin received within 48 h resulting in abnormally elevated aPTT above the upper limit of normal • Current use of anticoagulant with INR > 1.7 or PT > 15 s • Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (eg. aPTT, INR, platelet count, ECT, TT, or appropriate factor Xa activity assays) • Blood glucose concentration <50 mg/dL (2.7 mmol/L) • Computerized tomography demonstrates multilobar infarction
<i>Relative exclusion criteria</i> (consider risk-to-benefit ratio of intravenous rtPA administration if any of these relative contraindications is present):
<ul style="list-style-type: none"> • Minor or rapidly improving stroke symptoms (clearing spontaneously) • Pregnancy • Seizure at onset with postictal residual neurological impairments • Major surgery or serious trauma within previous 14 days • Recent gastrointestinal tract hemorrhage (within previous 21 days) • Recent urinary tract hemorrhage (within previous 21 days) • Recent acute myocardial infarction (within previous 3 months)

Notes: A physician with stroke management expertise in acute stroke care may modify this list. In rtPA candidates without recent use of oral anticoagulants or heparin, treatment with intravenous rtPA can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local laboratory standards. In rtPA candidates without a history of thrombocytopenia, treatment with intravenous rtPA can be initiated before availability of platelet count but should be discontinued if platelet count is <100,000/mm³

aPTT activated partial thromboplastin time, *ECT* ecarin clotting time, *INR* international normalized ratio, *PT* partial thromboplastin time, *rtPA* tissue-type plasminogen activator, *TT* thrombin time

need to be treated within 3 h and 14 patients need to be treated within 3–4.5 h for one extra person to have “mild to no disability” at 3 months [12]. The protocol for IV rtPA within the 3–4.5-h period is similar to that for acute intervention in the 0–3-h window. The criteria for selection of eligible patients have recently been loosened [10]. The following considerations apply for patients who are in the 3–4.5 h time window [10]:

- For patients taking oral anticoagulants with an INR < 1.7, *IV rtPA appears safe and may be beneficial*
- For patients with a baseline NIHSS score >25, *the benefit of IV rtPA is uncertain*
- For patients with a history of both stroke and diabetes mellitus, *IV rtPA may be as effective as treatment in the 0–3 h. window and may be reasonable*

Endovascular Therapy: 0–6 h

Intravenous rtPA is the first-line therapy for patients who meet the criteria. Endovascular therapy with stent retrievers should also be considered for patients within 6 h of symptom onset with an NIHSS score ≤ 6 and large-vessel occlusions documented on noninvasive imaging (Class I; Level A Recommendation) [4]. Most of the data on the benefit of endovascular recanalization involves patients who have received IV rtPA. Although the clinical efficacy of acute endovascular therapy is unclear for patients who have contraindications or fall out of the time window for IV rtPA, it is considered reasonable in carefully selected patients (Class IIa; Level C recommendation) [4]. Acute endovascular therapy requires that organized systems and infrastructure be in place, and it should be performed only at hospitals that can provide comprehensive stroke care.

Case Selection for Endovascular Therapy

Additional imaging beyond CT and CTA or MRI, and magnetic resonance angiography (MRA), such as CT perfusion or MR diffusion- and perfusion-weighted imaging, is often used for selecting patients for endovascular therapy, but currently is not required.

Characteristics of candidates for emergent endovascular recanalization include the following [4]:

Clinical

- prestroke modified Rankin Scale score ≤ 1
- NIHSS score ≥ 6
- treatment can be initiated (groin puncture) within 6 h of symptom onset
- age ≥ 18 years
- acute ischemic stroke receiving intravenous rtPA within 4.5 h of onset

Imaging

- Alberta Stroke Program Early CT score ≥ 6
- causative occlusion of the internal carotid artery or proximal middle cerebral artery

Management of Patients Receiving Acute Intervention

Patients receiving IV rtPA or endovascular intervention are at risk for hemorrhagic complications and should be followed closely in a step-down unit or neurointensive care unit (NICU). The same BP criteria should be used for patients undergoing endovascular recanalization unless specific situations warrant individualized management. In the absence of clinical data demonstrating otherwise, serial neurological assessments should be performed in all patients receiving endovascular intervention using the same protocol as for patients receiving IV rtPA.

Acute Inpatient Stay

Diagnostic Approach (Diagnostic Care Path)

Laboratory

A core set of laboratory tests should be performed in all patients admitted with ischemic stroke. They include a chemistry panel (electrolytes, renal function), (alanine transaminase (ALT), complete blood count including platelet count, cardiac enzymes, fasting lipid panel and HgA1C or fasting blood glucose. If HgA1C and a fasting lipid panel have been obtained in the past 30 days, additional testing may not be warranted.

Imaging

Determination of the stroke mechanism is necessary to initiate the appropriate secondary stroke prevention therapies. This entails diagnostic testing that includes the following:

Brain imaging—A brain MRI (with diffusion-weighted sequencing) should be considered. If patients are MRI ineligible, a noncontrast head CT is an acceptable alternative but may need to be repeated 24–48 h after symptom onset if initially negative for ischemia. Brain imaging can identify the extent and location of damage and provide some information about the possible stroke mechanism.

Vascular imaging—*Carotid imaging should be performed for all patients with acute ischemic stroke unless the stroke is clearly not in the distribution of the anterior circulation, patients are not candidates for carotid revascularization or carotid imaging has been recently performed prior to hospitalization [13].* Guidelines have variously recommended gadolinium-enhanced MRA of the neck, or CTA [14] and carotid ultrasound [15] for noninvasive imaging of the extracranial carotids.

Intracranial vascular imaging is also recommended if not done during the hyperacute stroke period. Either a CTA or MRA can be performed, which will help determine the stroke mechanism and the risk of recurrent stroke.

Other Ancillary Tests

Echocardiogram—A transthoracic echocardiogram (TTE) should be obtained for all patients with ischemic stroke who are candidates for anticoagulation therapy. Transesophageal echocardiography may be considered in patients < age 55, or when there is a cardioembolic pattern on imaging without other cause (i.e., atrial fibrillation). A TTE with agitated saline or a transcranial doppler with bubble study may be performed when an intracardiac or extracardiac shunt is being considered. An echocardiogram provides information on the functional status of the heart and can identify cardiac sources of embolism. A transesophageal echocardiogram (TEE) provides better visualization of the cardiac atria and valves and is used in selected patients when the heart is the suspected source of embolism.

Cardiac monitoring—As previously discussed, all patients should have a baseline EKG on admission and should have continuous cardiac monitoring for at least the first 24 h after admission and ideally throughout their entire stay. *If atrial fibrillation is not detected in the hospital and a cardiac source of embolism is suspected, consider prolonged (>=30 days) outpatient monitoring [16].*

Additional diagnostic procedures (e.g., cerebral angiogram, transcranial doppler testing, single photon emission computed tomography (SPECT) scan, lumbar puncture) and additional laboratory testing (e.g., high-sensitivity C-reactive protein, lipoprotein A, cardiolipin antibodies, lupus anticoagulant panel, hypercoagulability panel, toxicology screening, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)/notch genotyping and testing for Fabry disease) are performed based on patient and stroke characteristics.

Therapeutics (Treatment Care Path) (Fig. 6.2)

Patients with acute ischemic stroke should be admitted to a nursing unit with nurses who have training and experience in caring for patients with stroke. Stroke units are preferred, with dedicated teams of nursing, physical therapy, occupational therapy, speech therapy, case management and social workers. Outcomes of patients placed in stroke units are improved (NNT = 18; similar to the effectiveness of IV rtPA), and this benefit can be extended to nearly all patients with stroke [5].

Prevention of Neurological Worsening

Neurological examination findings can fluctuate in the first hours to days after stroke, with early neurological deterioration occurring in 13.9–32.2% of acute stroke patients [17]. Because of this, it is important to serially assess neurological impairment using a validated stroke severity scale, such as the NIHSS.

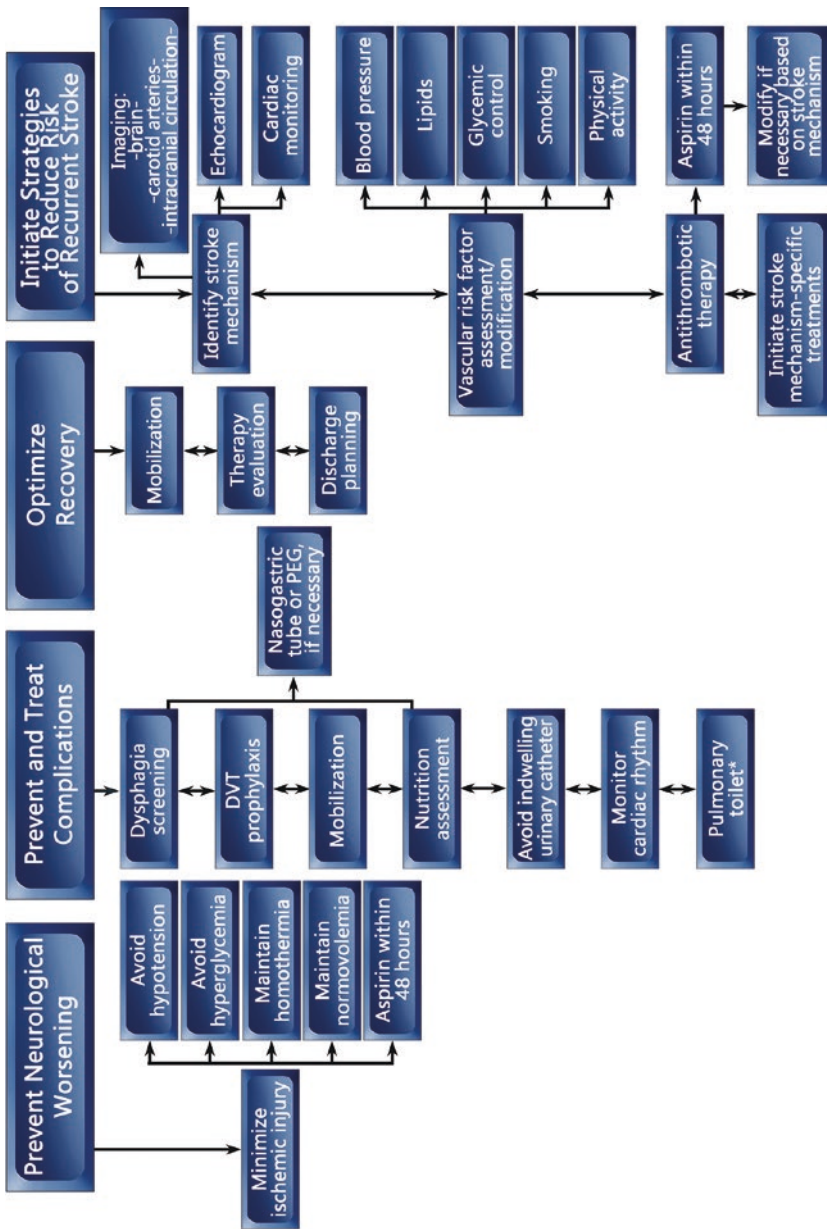


Fig. 6.2 Inpatient management of patients with ischemic stroke. *VTE* deep venous thromboembolism, *PEG* percutaneous gastrostomy tube. *Pulmonary toilet includes: elevation head of bed >30°, incentive spirometry, suction of secretions

Minimize Ischemic Injury

Cerebral perfusion should be optimized in the acute phase of stroke to minimize the extent of ischemic injury. Patients should be kept normovolemic. Because patients with acute stroke often do not have a normal oral intake of fluids, careful attention to hydration is necessary. Intravenous fluids, generally 0.9% normal saline, should be started at the time of initial presentation and continued as necessary. Blood pressure should also be carefully monitored in all patients. Generally, *home blood pressure medications should be withheld for the first 24 h after admission*. The initiation of antihypertensive agents depends on patient and stroke characteristics, but it should be considered after 24 h. Blood pressure exceeding 220/110 should be treated. The threshold for treatment with BP medication is lower for patients on anticoagulants who have received acute intervention. As described above, patients who receive IV rtPA, endovascular thrombolytic therapy or successful mechanical revascularization of an intracranial occlusion, or who are anticoagulated with either IV heparin or an oral anticoagulant, should have their blood pressure maintained at <180/105 mmHg. *Patients not receiving thrombolytic therapy, either intravenously or intra-arterially, and who are not therapeutically anticoagulated should receive 325 mg of aspirin within 24–48 h of stroke onset* (Class 1, Level A recommendation [7]).

Hyperthermia and hyperglycemia have both been associated with worse outcomes after stroke and should be treated. Treatment of fever should be swift and the source of the fever sought. Blood glucose levels should be maintained between 140 and 180 mg/dL (Class IIa, Level C recommendation [7]). More aggressive control of glucose levels in the hospital has been associated with worse outcomes [18].

Prevention of Complications

Complications after stroke are frequent and result in increased lengths of stay and worse clinical outcomes. Several standard processes should be followed in all stroke patients to minimize complication risk.

Dysphagia Screening

Dysphagia screening in stroke patients is critical to reduce adverse outcomes related to aspiration and inadequate hydration/nutrition. All patients presenting with neurological symptoms that may be due to stroke or TIA should undergo a swallow assessment prior to any oral intake, including medications (Class 1, Level B recommendation [7]).

Prophylaxis for Venous Thromboembolism (VTE)

Patients with stroke are at increased risk for the development of deep vein thrombosis. Unless a contraindication exists, ischemic stroke patients who are not anticoagulated should receive medical VTE prophylaxis (Class I, Level A recommendation

[7]). Enoxaparin has been shown to be slightly superior to unfractionated heparin in hospitalized patients with acute ischemic stroke [19], and it is the medication of choice. For patients who are at increased risk of hemorrhage, subcutaneous heparin, given TID or BID, may also be used. In addition, intermittent compression stockings (ICS) should be used on all patients, especially those who have a contraindication to medical prophylaxis (Class IIa, Level B recommendation [7]). The use of ICS in addition to medical prophylaxis further reduces the risk of VTE [20]. When intermittent compression stockings are used, they should be worn whenever the patient is in bed, both day and night.

Mobilization

Early mobilization of less severely affected patients is recommended (Class I, Level C recommendation [7]). Ideally, patients should be out of bed or in an upright position at least three times per day.

Nutrition Assessment

Patients who cannot take solid food and liquids orally should receive nasogastric (NG), nasoduodenal or percutaneous endoscopic gastrostomy (PEG) tube feeding to maintain hydration and nutrition while undergoing treatment to restore swallowing (Class I, Level B recommendation [7]). Nutritional intake should be continually monitored to ensure adequate nutrition, which is important to optimize recovery. The use of an NG tube is reasonable for the first 2–3 weeks after stroke (Class IIa, Level B recommendation [7]), although many post-acute care facilities will not accept patients with NG tubes in place. A PEG tube is another option for patients who will have prolonged impairment in swallowing and may be necessary for patients with severe neurological impairment or brainstem stroke.

Prevention of Hospital-Acquired Infections

Pneumonia is the most frequent serious complication after stroke and is associated with a three-fold increase in risk of mortality [21]. Early mobilization, aspiration precautions and pulmonary hygiene are important aspects of hospital care and include keeping the head of the bed elevated more than 30°, suctioning of secretions, incentive spirometry and bronchodilator treatments as necessary. Routine placement of indwelling bladder catheters is not recommended because of the associated risk of catheter-induced urinary tract infections (UTIs) (Class III, Level C recommendation [7]). The patient should be assessed for UTI if there is a change in the level of consciousness and no other cause of neurological deterioration is identified. Urine analysis should be used for initial screening and a culture obtained only if the urinalysis is positive.

Cardiac Monitoring

Myocardial injury, as identified by elevations of serum troponin (>0.1 $\mu\text{g/L}$) occurs in up to 20% of patients with acute stroke [22], and 2–3% of patients hospitalized with acute stroke have an associated acute myocardial infarction during their hospitalization, putting them at risk for potentially dangerous cardiac arrhythmias [23]. Cardiac monitoring can help identify the occurrence of paroxysmal atrial fibrillation, a significant cause of ischemic stroke. Patients should have continuous cardiac monitoring for at least the first 24 h after admission and ideally throughout their entire stay (Class B, Level 1 recommendation [7]).

Hemorrhagic Transformation

According to recent acute stroke management guidelines, symptomatic hemorrhage occurs in approximately 5–6% of patients after IV rtPA, endovascular therapy or anticoagulant use [7]. In patients with hemorrhagic conversion or new intracranial hemorrhage who have received thrombolysis within the past 24 h, rtPA reversal should be instituted.

Reducing Risk of Recurrent Stroke

Vascular Risk Factor Modification

Thorough assessment of vascular risk factor status and initiation of appropriate therapies should be done during hospital admission. The main risk factors are outlined below.

Blood Pressure

Hypertension is the most important modifiable risk factor and has a populational attributable risk for all stroke of 34.6% (ischemic and hemorrhagic) [24]. Antihypertensive medications have been shown to reduce the risk of recurrent stroke. The American Heart Association has recently revised their recommendations and endorse initiation of antihypertensive therapy if patients have $\text{SBP} \geq 140$ mmHg or $\text{DBP} \geq 90$ mmHg (Class IIb; Level of Evidence C recommendation) [16]. Resumption of BP therapy is indicated for previously treated patients with known hypertension. Diuretics, and angiotensin converting enzyme inhibitors (ACEIs) have specifically been shown to be beneficial. Other agents, such as calcium-channel blockers, alpha adrenergic blockers and beta-blockers, are additional options. The short-term goal of BP control is a reduction of 10/5 mmHg [7]. The long-term goal should be a BP of $<140/90$ mmHg, or $<130/80$ mmHg in patients

with diabetes or chronic kidney disease [25]. Many patients will require more than one agent to obtain control.

Lipids

Several studies have demonstrated an association between elevated low density lipoprotein (LDL) and stroke risk, and the administration of a high-intensity statin has been shown to reduce recurrent vascular events in patients with atherosclerotic cardiovascular disease [26], including patients with stroke [27]. Regardless of LDL levels, patients with stroke presumed to be of atherosclerotic origin should be placed on high-intensity statin therapy, either ≥ 40 mg atorvastatin or ≥ 20 mg rosuvastatin [16].

Glycemic Control

Diabetes is an independent risk factor for stroke and cardiovascular disease. Blood glucose should be carefully monitored with a goal of HgbA1C $< 7\%$ for most patients [28].

Smoking

Patients who have smoked in the last year should be advised to quit (Class I, Level C recommendation [16]). They should receive educational materials and/or formal smoking cessation counseling, or medications to assist with smoking cessation.

Physical Activity

Stroke patients should be advised to engage in physical activity as tolerated. They should be referred to a comprehensive behaviorally oriented program if they are able and willing to increase their physical activity. At least 3–4 sessions per week of moderate to vigorous -intensity exercise that last approximately 40 min is recommended (Class IIa, Level C recommendation [16]).

Antithrombotic Use

Choice of antithrombotic medications, as with other aspects of stroke care, must be individualized for each stroke patient. A comprehensive discussion of antithrombotic therapies to address a specific mechanism of stroke is beyond the scope of this care path. In general, the use of intravenous heparin or other anticoagulants to prevent early stroke recurrence or to prevent neurological deterioration is not warranted. Anticoagulation should be used, however, for *long-term* prevention of recurrent

stroke in patients with atrial fibrillation. Warfarin, dabigatran or apixaban are all indicated for long-term anticoagulation in patients with atrial fibrillation [16]. Rivaroxaban is also reasonable [16]. These are typically started at the time of discharge or two to four weeks after stroke onset, depending on the size of the infarct and the risk of hemorrhagic conversion. If warfarin is used, bridging with intravenous heparin is generally not indicated [7]. In most situations, patients should be placed on aspirin until INR becomes therapeutic (“aspirin bridge”). For patients with noncardioembolic stroke, antiplatelet agents should be used, either aspirin (50 mg, 81 mg or 325 mg), clopidogrel or the combination of extended-release dipyridamole BID plus aspirin 25 mg BID [16]. For patients who have a stroke while on an antiplatelet agent, there are little data to demonstrate that switching from one antiplatelet agent to another is more effective at reducing recurrent stroke risk. The 2014 American Heart Association guidelines on secondary stroke prevention also indicate that the combination of aspirin and clopidogrel “might be considered” for initiation within 24 h of a minor ischemic stroke or transient ischemic attack (TIA) and for continuation for 90 days (*Class IIb; Level of Evidence B recommendation*) [16].

A more extensive discussion of vascular risk factor control and management according to stroke mechanism is beyond the scope of this care path but is available in the American Stroke Association 2014 Guidelines for Secondary Prevention of Ischemic Stroke and TIA [16].

Optimize Recovery

Mobilization

Early mobilization is also an important component to improve stroke recovery, although the specific timing that mobilization should begin is unknown.

Therapy Evaluation

Physical and occupational therapy evaluation and management should be ordered for all ischemic stroke patients who have persistent functional impairments and who are not on bed rest. They provide rehabilitative services and input on appropriate discharge destination. Patients with severe strokes will benefit from range of motion exercises. Speech therapy should be ordered for patients with speech disturbance or impairment of swallowing.

Discharge Planning

Discharge planning includes the identification of discharge destination, education of patients and caregivers regarding stroke symptoms and ways to reduce recurrent events, communication to other providers and post-discharge facilities, and scheduling follow-up appointments.

Post-Discharge Management

Because the initial time period after stroke is a high risk period for post-stroke complications, readmission and depression, patients should ideally be seen by their primary care provider within one week of hospital discharge and by their neurologist within 30 days. Although this care path focuses on the acute ischemic stroke admission, patients who have had an acute ischemic stroke require close monitoring and care throughout their life.

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Chapter 7

Vascular Cognitive Impairment and Vascular Dementia

Aaron Ritter and Jagan A. Pillai

Clinical Pearls

- The clinical triad of urinary incontinence, gait disturbance, and cognitive decline—commonly associated with normal pressure hydrocephalus (NPH)—is more often due to cerebrovascular disease [1].
- Although no neuroimaging criteria have been developed to define a threshold of white matter involvement sufficient to cause VaD, several experts and clinical trials have used a threshold of 25% involvement (of total white matter) for defining VaD [2].
- There are no medications specifically approved for use in VaD, however, patients with VaD may benefit from a trial of a cholinesterase inhibitor and/or memantine. General principles of pharmacological management of VaD follow those of the pharmacological management of AD: slow titration to maximum doses, using only one cholinesterase inhibitor at a time, adding memantine to cholinesterase therapy in the moderate to severe stages of disease.

Introduction

Cerebrovascular disease is an important cause of cognitive dysfunction, second only to Alzheimer's disease (AD) as a cause of dementia in the elderly [3]. The construct of dementia due to cerebrovascular disease has evolved over time and a

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number of different terms have been used including Binswanger's disease, multi-infarct dementia, and post-stroke dementia. These terms were often inconsistently applied and focused solely on memory dysfunction. Presently, the preferred term is vascular cognitive impairment (VCI) because it captures the entire spectrum of cognitive impairment attributable to cerebrovascular disease and also acknowledges the impact that vascular lesions have on the expression of other neurodegenerative processes (mixed syndromes) [4]. In its mildest form, VCI affects a single cognitive domain and independent functioning is preserved. In its most severe form, multiple cognitive domains are impaired and patients are described as having vascular dementia (VaD). VaD is caused by a variety of pathologies, and can present clinically with multiple phenotypes. Current diagnostic criteria require the clinician to establish a clear relationship (temporal, severity, or cognitive pattern) between the presence of vascular disease and cognitive impairment. It is still unclear, however, whether identified vascular lesions are the sole cause of cognitive dysfunction, are contributing to the expression of other disease processes, or are present but not impacting cognitive function. More recently, multiple autopsy studies have also shown that microinfarcts, which are not readily by currently used 1.5 T and 3 T magnetic resonance imaging (MRI) and noted in 7 T MRI, are major risk factors for cognitive impairment.

Determining the threshold of cerebral tissue damage required to cause dementia has proven difficult and there are no established pathological criteria for VaD as there are for other neurodegenerative diseases. There is, however, strong evidence that the likelihood of cognitive dysfunction increases with both lesion volume and number [5]. This, along with prospective cohort studies showing that recurrent stroke is a major independent risk factor for dementia [6], suggests that the course and prognosis of VaD is strongly related to additional vascular injury. Because the risk factors for and secondary prevention of cerebrovascular disease are well established, interventions for VaD may have a greater clinical impact than for other neurodegenerative disorders. Accurate assessment and management of vascular risk factors are, thus, a priority in the treatment of VaD. Although there are no approved therapies to overcome cognitive impairment in VaD, several agents used for AD have demonstrated modest cognitive benefits. A trial of one of these agents as well as proper management of any neuropsychiatric symptoms that emerge during the disease course are important components of the symptomatic management of VaD.

Epidemiology

While studies vary greatly, many experts believe that cerebrovascular disease is responsible for 10–20% of all dementia cases [3, 4]. The estimated prevalence rate of VaD is between 1 and 4% of individuals over the age of 65 [7]. Like AD, VaD is strongly age related, with prevalence rates doubling every 5.3 years after age 65 [4]. In individuals over the age of 85, the prevalence of VaD approaches that of AD [8]. Mixed dementia syndromes including cerebrovascular disease co-occurring with AD, Lewy bodies, or frontotemporal pathology are increasingly recognized. 25–80% of elderly dementia patients show mixed pathologies on autopsy [9].

Risk Factors

A large body of evidence has demonstrated the significant relationship between stroke and dementia. In general, having a stroke doubles the risk of developing dementia [4]. Risk factors for dementia after stroke include increasing age, low education status, diabetes, atrial fibrillation, stroke location (particularly left hemisphere), the presence of multiple strokes, and temporal lobe atrophy (suggestive of concurrent AD pathology) [10]. In the absence of clinical stroke, advancing age and vascular risk factors are associated with an elevated risk of VaD [11]. Additional risk factors linked to VaD—physical inactivity, the metabolic syndrome, smoking, stroke—are also risk factors for AD and suggest a possible shared pathophysiology [12].

Clinical Manifestations

The clinical manifestations of VaD are diverse and may include a wide variety of cognitive, behavioral, and/or physical changes. Several factors influence clinical presentation including the location of injury, volume of tissue injured, pathology causing the injury (i.e. hemorrhagic vs. ischemic), presence of concurrent neurodegenerative diseases, and time between brain injury and clinical evaluation. Table 7.1 lists the main VaD subtypes. The cognitive changes in VaD can generally be divided into two patterns—one in which the clinical features are attributable to damage to the large vessels supplying the cerebral cortex (cortical dementia) and one in which chronic ischemic and infarction of smaller vessels results in clinical features attributable to damage to subcortical structures (subcortical dementia) [13]. Although helpful conceptually, these patterns are not always mutually exclusive, and it is not uncommon for patients to present with features of both types of dementias.

Cortical Dementia

Cortical dementia is caused by repeated infarcts (multi-infarct dementia) or single infarctions (strategic infarct dementia) of the large vessels supplying functionally important cortical brain regions. In VaD caused by multiple infarctions, the location, number, and volume of tissue damaged determines the pattern of cognitive and behavioral change [5]. Lesions involving the anterior, middle, or posterior cerebral arteries supplying large vascular territories can give rise to well-known dementia syndromes [14]. With injury to the left hemisphere, apahasias, apraxias, agnosias and elements of Gerstmann syndrome (agraphia, acalculia, left-right disorientation, finger agnosia) are often manifest while injury to the right hemisphere may result in neglect, confusion, aparaxias and constructional difficulties. Table 7.2 describes

Table 7.1 Subtypes of vascular dementia

Subtypes	Vessels involved	Common causes	Associated brain lesions
Strategic infarct dementia	Large and medium sized arteries and arterioles	Arterial occlusion due to thrombotic atherosclerosis or embolization	Single infarcts in functionally important areas: hippocampus, caudate, angular gyrus, thalamus
Multi-infarct dementia	Large and medium sized arterioles	Arterial occlusion due to thrombotic atherosclerosis or embolization	Multiple cortical or subcortical lesions (cortical, lacunar, microinfarcts)
Lacunar state (<i>etat lacunaire</i>)	Arterioles	Arteriolo sclerosis, lipohyalinosis	Multiple lacunar infarcts in the basal ganglia and internal capsule
Subcortical leukoencephalopathy (Binswanger's disease)	Arterioles and small vessels	Arteriolo sclerosis, lipohyalinosis, venous collagenosis	Lacunar infarcts in basal ganglia and frontal lobe white matter; diffuse white matter disease
Hypoperfusion dementia	Large arteries	Cardiac failure, carotid occlusion	Watershed infarcts, incomplete white matter infarcts, cortical laminar necrosis
Hemorrhagic dementia	Arteries, arterioles, veins	Arterial or venous rupture	Lobar or basal ganglia hemorrhage, subdural, subarachnoid, or intracerebral hemorrhage
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	Arterioles and small vessels	Notch 3 mutation	Lacunar infarcts in basal ganglia and frontal lobe white matter; diffuse white matter disease
Cerebral amyloid angiopathy	Arterioles and small vessels	Amyloid fragment deposition in arteries and arterioles	Lobar hemorrhage, microinfarcts, microhemorrhage, white matter lesions; typically spare basal ganglia

several of the well-known regional cognitive syndromes. The cognitive profile of post-stroke dementia is characterized by variable impairments across cognitive domains [15]. As a result, the term “patchy” is often applied to describe the cognitive pattern of severe deficits in certain domains and relative sparing of others. In cortical dementia, memory may be preserved, especially if the vascular supply to the medial temporal lobes is spared. Because the source of infarction is typically cardiac embolization or thrombotic atherosclerosis, symptom onset may be abrupt. If the primary motor cortex is spared, however, symptoms typically attributed to stroke may not be clearly noted. It is not uncommon for patients to stabilize or even improve after each stroke, resulting in a “stepwise” clinical course. With recurrent events, the vascular burden accrues and the dementia syndrome emerges.

Table 7.2 Cortical syndromes

Lateralization	Lesion	Possible symptoms
Left	Anterior cerebral	Akinetic mutism, disinhibition, abulia, apathy, executive dysfunction, callosal disconnection
	Middle cerebral	Aphasia, Gerstmann's syndrome (agraphia, acalculia, finger agnosia, right/left disorientation)
	Posterior cerebral	Alexia without agraphia, homonymous hemianopia
Right	Anterior cerebral	Apathy, abulia, executive dysfunction, behavior change, mania, callosal disconnection syndrome
	Middle cerebral	Hemineglect, anosognosia, constructional difficulty, confusion, agitation, visuospatial difficulty
	Posterior cerebral	Prosopagnosia, homonymous hemianopia

Subcortical Dementia

Subcortical dementia is caused by the cumulative effects of occlusive disease affecting the medium-sized arterioles and small vessels supplying the basal ganglia and subhemispheric white matter. Strongly associated with vascular risk factors, subcortical lesions are the most common lesions associated with VaD [9]. On MRI, small vessel disease is manifest as multiple lacunar infarcts (small noncortical infarcts measuring less than 1.5 cm) or areas of confluent white matter disease (also called leukoariosis). Over time, the accumulated effect of these lesions is to disrupt subcortical and limbic circuits leading to a slowly progressive syndrome characterized cognitively by executive dysfunction, slowed mentation (bradyphrenia), and attentional deficits. Memory dysfunction is commonly manifest in subcortical dementia [16]. The pattern of memory loss is typically one of poor registration and inefficient retrieval rather than the “rapid forgetting” that is seen in AD. As a result, patients with subcortical VaD are more likely to benefit from hints or cues and perform better on recognition memory tasks [17]. Behavioral changes such as irritability, depression, and apathy are often among the most striking and earliest symptoms seen in subcortical dementia. The neurological examination of a patient with VaD due to subcortical injury is often described as “lower body parkinsonism” due to gait changes and falls. Patients often manifest with *marche a petit pas* (“gait with little steps”), a gait characterized by abnormally short, shuffled steps with upright stance and preserved arm swing. The face and upper extremities are typically less affected, however, careful examination of the upper extremities often reveals cogwheel rigidity or even spasticity. Another common feature of subcortical VaD is bladder dysfunction (frequency, urgency, and incontinence) not explained by urological disease. The triad of urinary incontinence, gait disturbance, and memory loss is more commonly produced by VaD than hydrocephalus [1].

Table 7.3 Neuropsychiatric symptoms associated with focal brain lesions

Symptom	Lesion
Apathy/abulia	Bilateral medial frontal
	Globus pallidus
	Medial thalamus
Disinhibition	Orbitofrontal
	Caudate
Depression	Left frontal
Anxiety	Left frontal
Obsessions and compulsions	Caudate
	Bilateral globus pallidus
Anosognosia	Right parietal
Mania	Right frontal

Neuropsychiatric Features

As in other dementia syndromes, neuropsychiatric symptoms are experienced almost universally in VaD [13] and represent a significant source of distress for both patients and their families. Apathy, depression, and abulia are considered hallmark neuropsychiatric features of subcortical VaD. Depression is frequently encountered after stroke with a cumulative incidence of 39–52% within 5 years of stroke [18]. Left frontal stroke is traditionally associated with an increased risk of post-stroke depression [19]. Other neuropsychiatric symptoms are experienced in VaD and may correlate to lesion location. Table 7.3 lists neuropsychiatric symptoms commonly associated with focal brain lesions. In comparison studies, patients with VaD experience more severe depression and apathy and are less likely to experience delusions or hallucinations than patients with AD [20].

Diagnostic Approach

Cognitive Screening

While cognitive deficits can be evaluated with questioning during the history, patients and family members often underestimate the severity of cognitive impairment and objective assessment of cognitive functioning is important. There are many bedside cognitive tests available to screen for dementia. The Mini-Mental Status Examination (MMSE) is the tool most commonly administered in the office setting. Designed to detect cognitive changes in AD, the MMSE lacks an assessment of executive function and is less sensitive to the early cognitive changes seen in VaD [21]. Other tests which more closely examine executive function, attention, and visuospatial function, such as the Montreal Cognitive Assessment (MoCA), are more likely to identify cognitive dysfunction in this population [22, 23]. The MoCA

includes a more detailed examination of memory (with sections on registration and both free and cued delayed recall) than the MMSE. The Vascular Dementia Assessment Scale (VADAS-cog) is another tool that has been used in clinical trials of patients with VaD and shows good sensitivity in patients even in patients with mild disease burden [24]. Deficits appreciated on screening tests can be further investigated with additional domain-specific tests and referral for neuropsychological evaluation.

Neuropsychiatric Assessment

Patients being evaluated for dementia should also be screened for neuropsychiatric symptoms as these symptoms often represent a significant source of distress for patients and families. Patterns of neuropsychiatric symptoms may also inform the differential diagnosis. The neuropsychiatric assessment can be supported by symptom rating scales, inventories and caregiver scales. Commonly used screening tools include the Neuropsychiatric Inventory Questionnaire (NPI-Q) [25], the Geriatric Depression Scale (GDS) [26], and the Behavioral Rating Scale for Dementia [27].

Functional Assessment

Assessment of activities of daily living is critical in a comprehensive evaluation of patients with dementia. Establishing a baseline is crucial in following the progression of disease and monitoring response to treatment. Accurate assessment of functional status will also direct both appropriate pharmacological and non-pharmacological interventions. Commonly used assessments include the Instrumental Activities of Daily Living Scale [28] and the Functional Activities Questionnaire [29].

Laboratory

There are no available blood or cerebral spinal fluid tests specific to the diagnosis of VaD. Laboratory testing can be used to rule out mimics (hypothyroidism, B12 deficiency), as well as to identify risk factors that may be contributing to cerebrovascular disease burden. Table 7.4 lists the laboratory tests that should be obtained in patients with suspected VaD. Homocysteine is particularly relevant in VaD due to its putative prothrombotic properties. Elevated homocysteine levels are associated with an increased risk of cerebrovascular disease and VaD [31, 32]. Vitamin supplementation with folate, B6, and B12 lowers homocysteine levels by about 20% [33] but has not been shown to prevent cognitive decline or improve cognition in VaD [34].

Table 7.4 Recommended laboratory screening in the initial workup of patients with VaD

Complete blood count
Comprehensive metabolic panel
Thyroid function panel
Homocysteine and methylmalonic acid
B1 (thiamine)
B9 (folic acid)
B12 (cobalamin)
Vitamin D
RPR/VDRL, HIV, hepatitis panel (if high level of suspicion)
Erythrocyte sedimentary rate
Inflammatory/autoimmune lab panel (if high level of suspicion)
Testosterone (in men with suggestive history) [30]

Neuroimaging

MRI and CT

Neuroimaging is essential for the diagnosis of VaD and required by most diagnostic schemes. All patients with clinical features suggestive of VaD—clinical stroke, focal neurological findings, abrupt symptom onset or stepwise disease course—should have neuroimaging. Although computed tomography (CT) scan may reveal large chronic infarcts or extensive white matter disease, magnetic resonance imaging (MRI) is the modality of choice as it provides better sensitivity in identifying smaller subcortical lesions not easily seen on CT. Unless there is increased suspicion of mass lesion or tumor, initial scans are usually obtained without contrast. The neuroimaging hallmarks of VaD include cortical infarcts, hemorrhage, lacunar infarcts, and white matter hyperintensities (also referred to as leukoaraiosis). Figure 7.1 shows several MRI findings commonly seen in VaD. Although there are no radiologic criteria for the diagnosis of VaD, the presence of dementia often correlates with overall vascular burden [10]. White matter hyperintensities seen on T2 or fluid attenuated inversion recovery (FLAIR) MRI sequences are commonly seen in both cognitively normal and demented populations and the interpretation of these lesions is not completely understood. Smooth periventricular rims and punctate lesions have less clinical significance than irregular confluent white matter hyperintensities, which, in elderly patients with vascular risk factors, are likely to represent a variety of vascular-mediated pathological processes (loss of myelin, microglial, and inflammatory changes) [35, 36]. White matter lesions have also been associated with demyelination, infection, neoplasms, and migraine, necessitating careful clinical correlation. In

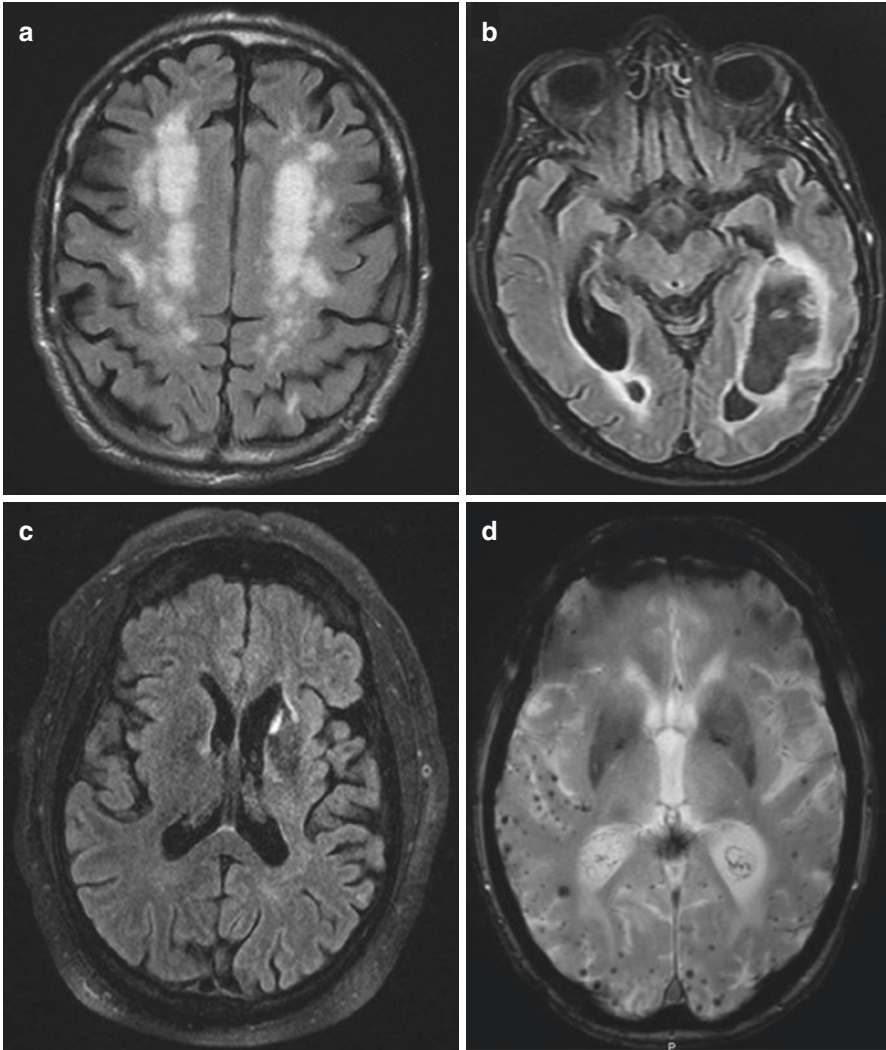


Fig. 7.1 MRI findings in VaD. (a) Confluent white matter changes related to small vessel disease on FLAIR imaging sequence in a patient with Binswanger's disease. (b) Left temporal-parietal lobar hemorrhage with subsequent alexia as a striking cognitive deficit on FLAIR imaging sequence. (c) Left caudate infarct in a patient with strategic infarct dementia resulting in executive dysfunction following disruption of frontal subcortical circuits on FLAIR imaging sequence. (d) Multiple cortical microhemorrhages in a patient with cerebral amyloid angiopathy on a T2* sequence

clinical trials and research studies, radiologic evidence of 25% involvement of cerebral white matter is often used as a threshold to identify VaD [2].

Microinfarcts are increasingly recognized as significant contributors to cognitive dysfunction in dementia populations. In the Religious Orders Study, the presence of microinfarcts was associated with increased risk of dementia and reduced speed and poorer memory performance on cognitive testing. This is of particular relevance because microinfarcts fall below the resolution of currently used 1.5 and 3 T MRI and approximately 50% of people with microinfarcts do not have macroinfarcts [37]. Improving the diagnostic sensitivity of VaD remains a major goal in the field [36].

FDG-PET and Amyloid Imaging

Fluorodeoxyglucose positron emission tomography (FDG-PET) is not routinely obtained in the evaluation of VaD as structural imaging is usually adequate for diagnosis. FDG-PET may be useful in confirming the presence of concurrent neurodegenerative pathologies. Certain patterns of hypometabolism: parietal and posterior cingulate in AD; frontotemporal in FTD; and mesial occipital cortex in DLB, should alert the clinician to the likely presence of a mixed syndrome.

Amyloid PET is available as a means of excluding AD as a contributing factor in a patient with suspect VaD (Fig. 7.2) or as means of supporting the presence of AD in a patient with mixed dementia.

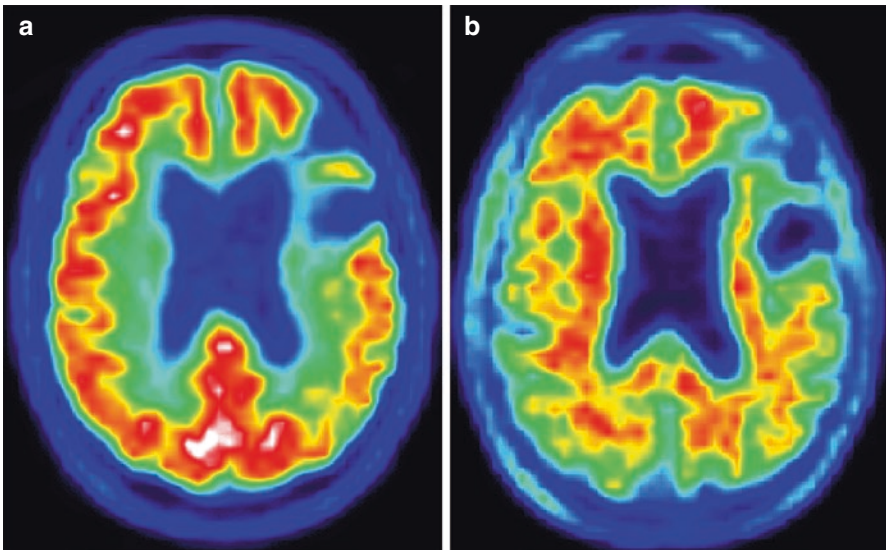


Fig. 7.2 FDG PET (a) (left) in a patient with VaD and no AD as shown by negative amyloid imaging (b) (right)

Electrophysiology

Electrophysiology is neither sensitive nor specific in the diagnosis of VaD. Stroke, however, is the most common antecedent factor for the development of epilepsy in adults [38]. “Red flag symptoms” suggestive of seizure disorder overlap considerably with the symptoms of VaD and include abrupt and stereotyped changes in behavior, repeated episodes of incontinence, and fluctuating cognition. A low threshold of clinical suspicion should lead to obtaining an electroencephalogram (EEG).

Genetic Testing

Genetic testing is of limited value in older patients (>65 years of age) with VaD. In younger patients presenting with VaD, a rare but important cause is cerebral autosomal dominant arteriopathy (CADASIL). This disorder is caused a mutation in the NOTCH3 gene on chromosome 19. Patients with CADASIL develop extensive lacunar infarctions and white matter disease before the age of 60 (Fig. 7.3). Inheritance is autosomal dominant. Common features associated with CADASIL include migraine with aura, repeated TIAs, and seizures. White matter lesions involving the anterior pole of the temporal lobe are distinct features of CADASIL and rarely seen in patients with ischemic disease [39]. A commercially available test is available to test for the NOTCH3 mutation and should be considered for appropriate patients.

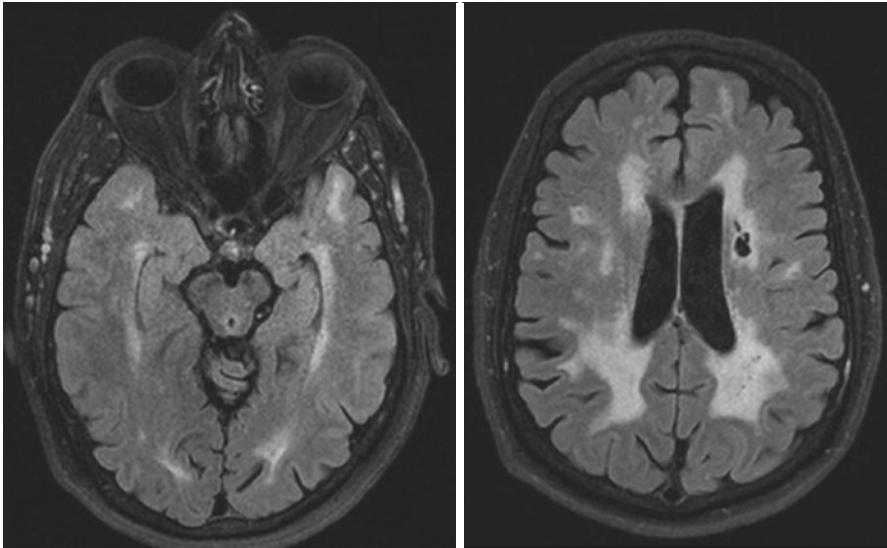


Fig. 7.3 MRI of 57 year old male with CADASIL

Table 7.5 Characteristic patterns of cognitive impairment in dementing disorders

Syndrome	Cognitive deficits
Alzheimer's disease	Memory (encoding, retrieval, recognition)
	Executive function
	Visuospatial deficits
Frontotemporal dementia	Executive function
	Variable language impairment
Dementia with Lewy bodies	Attention and concentration
	Visuoperceptual deficits
	Visuoconstructional deficits
Vascular dementia	Attention and concentration
	Memory (retrieval)
	Executive function

Neuropsychological Testing

Formal neuropsychological testing provides reliable information on a patient's cognitive functioning. This can be valuable in the care of VaD as it can be used to track the evolution of cognitive deficits over time and to monitor response to treatment. Testing can also be used to aide in the differential diagnosis given the different patterns of cognitive deficits seen in other dementing disorders. Table 7.5 summarizes the different patterns of neurocognitive performance among the various dementia syndromes. The neuropsychological pattern of AD overlaps considerably with VaD, however, differences in memory impairment—in AD memory deficits are seen in encoding and retrieval while in VaD deficits are primarily seen in retrieval—and executive function (greater impairment in VaD than AD) may be helpful in distinguishing the two [40].

Not all patients should be referred for formal neuropsychological testing. Neuropsychological testing is most helpful early in the course of illness when it is often difficult to distinguish from normal aging or when bedside screening tests fail to demonstrate the presence of deficits. The utility of neuropsychological testing in patients with moderate to advanced dementia is limited as performance on cognitive deficits is at "floor" levels.

Diagnostic Criteria

Several different clinical criteria for VaD have been proposed. A significant barrier in validating these criteria is the lack of standardized pathological criteria for VaD and the high co-occurrence of other pathologies in those with cerebrovascular disease. Earlier iterations of the diagnostic criteria for VaD required the presence of

Table 7.6 American Heart Association/American Stroke Association statement on vascular contributions to cognitive impairment and dementia clinical criteria for diagnosis of vascular dementia [4]

A diagnosis of probable vascular dementia requires either:
1. A clear temporal relationship between a vascular event and onset of cognitive deficits
or
2. A clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular pathology
and
3. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder
A diagnosis of possible vascular dementia requires imaging evidence of cerebrovascular disease but:
1. There is no clear relationship between the vascular disease and cognitive impairment or
2. There is insufficient information for the diagnosis of VaD or
3. Severity of aphasia precludes proper cognitive assessment or
4. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition

memory impairment for the diagnosis of dementia, a cognitive feature that is not always present in patients with VaD. In an attempt to recognize the broad contributions of vascular lesions on cognitive function from all causes (multi-infarct, subcortical, hemorrhagic), the more inclusive term of vascular cognitive impairment (VCI) has been introduced [4]. VCI captures the entire spectrum of cognitive impairment from mild impairment to dementia. The criteria also recognize the contribution of cerebrovascular disease to mixed dementia syndromes. For dementia due to VCI, at least two cognitive domains must be impaired and patient must meet functional impairment criteria for dementia (Table 7.6).

Differential Diagnosis

Clinically, the differential diagnosis of VaD includes other causes of cognitive impairment in the elderly including AD, Parkinson's disease, normal pressure hydrocephalus (NPH), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), human immunodeficiency virus (HIV) dementia, cerebral amyloid angiopathy (CAA), and Creutzfeldt-Jakob disease (CJD). These conditions can often be reliably excluded by correlating findings from the clinical examination to vascular lesions on neuroimaging. Figure 7.4 provides an approach to differential diagnosis. The Hachinski Ischemic Score (HIS) was initially established to distinguish multi-infarct dementia from AD and has historically been used to distinguish multi-infarct dementia from other dementia syndromes (Table 7.7). In a large meta-analysis including only studies with pathological

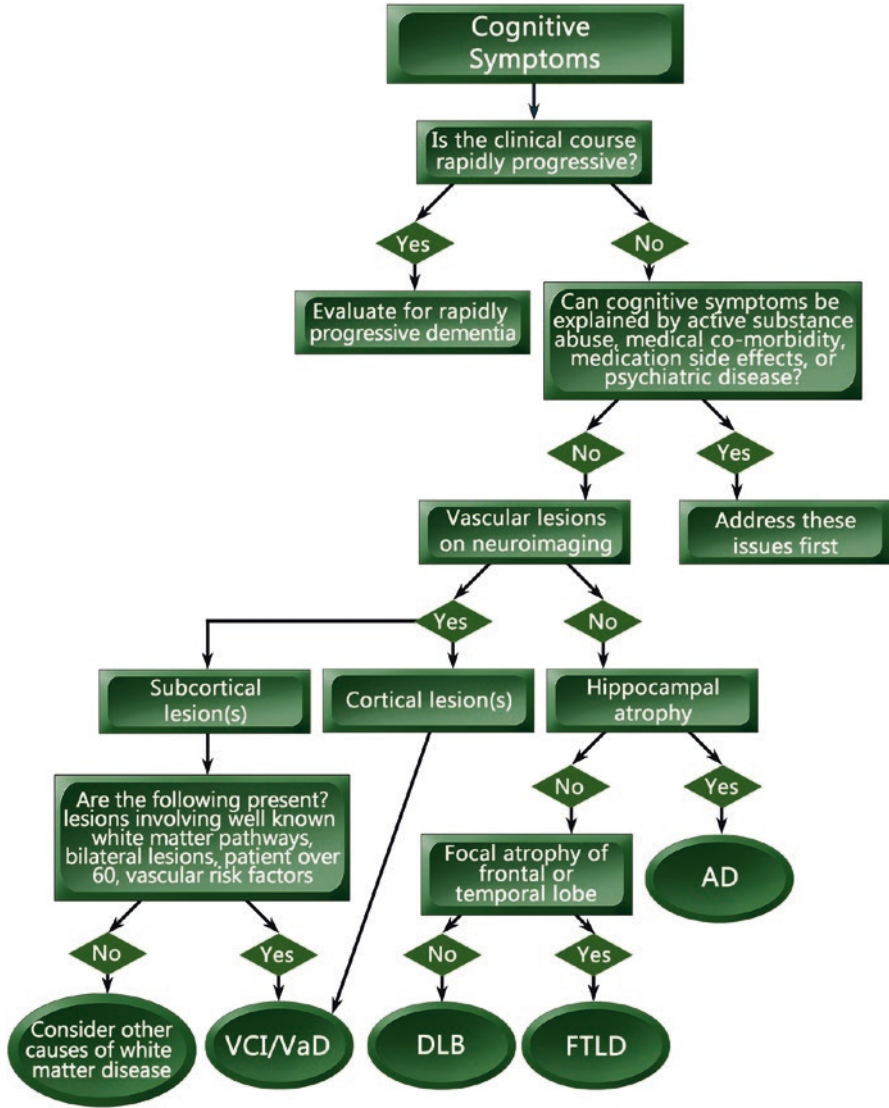


Fig. 7.4 Approach to dementia differential diagnosis

verification, a score of 7 or greater on the HIS had a sensitivity and specificity of 90% for VaD [41]. The HIS does not reliably distinguish pure VaD from mixed syndromes.

Table 7.7 Hachinski Ischemic Score

Symptom	
Abrupt onset	+2
Fluctuating course	+2
History of stroke	+2
Focal neurological symptoms	+2
Focal neurological signs	+2
Stepwise deterioration	+1
Nocturnal confusion	+1
Preservation of personality	+1
Depression	+1
Somatic complaints	+1
Emotional incontinence	+1
Hypertension	+1
Associated atherosclerosis	+1
Scores of 4 or lower suggest AD	
Scores of 7 or higher suggest VaD	

Table 7.8 Other causes of extensive white matter disease

Leukodystrophies	Metachromatic leukodystrophy, adrenoleukodystrophy, globoid cell leukodystrophy, cerebrotendinous xanthomatosis
Inflammatory disorders	Multiple sclerosis, systemic lupus erythematosus, sarcoidosis
Toxic or metabolic disorders	Cranial irradiation, solvent exposure, carbon monoxide poisoning, B12 deficiency, Marchiafava-Bignami disease
Neoplasms	Gliomatosis cerebri, primary cerebral lymphoma

The widespread white matter changes associated with subcortical VaD must be distinguished from non-ischemic causes of white matter hyperintensities on MRI. Some disorders causing non-ischemic white matter disease may also present with a progressive cognitive and behavioral impairment. The differential diagnosis for extensive subcortical white matter disease is large and includes the adult-onset leukodystrophies, infectious disorders, multiple sclerosis, inflammatory diseases, toxic or metabolic disorders, hydrocephalus, and neoplasms (Table 7.8). The characteristic appearance of white matter hyperintensities due to ischemic causes include confluent areas that are often bilateral and symmetrically located in the hemispheric white matter [42]. They are most commonly symmetrical, supratentorial, and periventricular [43]. Figure 7.5 provides an approach to assessing VCI.

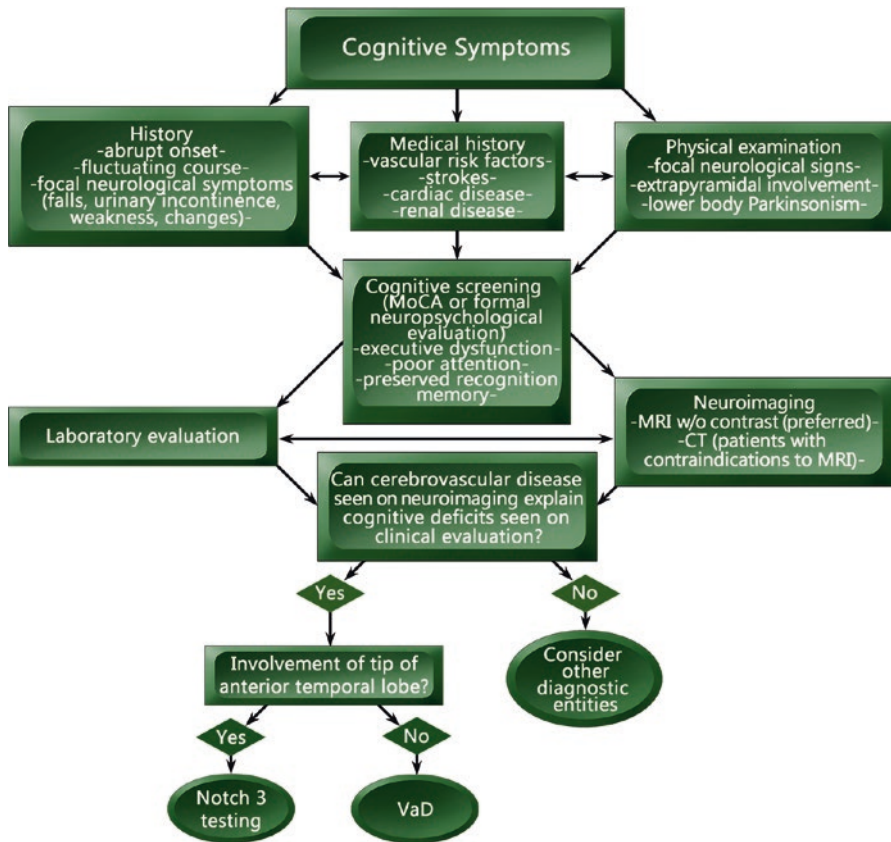


Fig. 7.5 Assessment of VCI

Management

Currently there are no therapies that can reverse the cerebrovascular damage that causes VaD. The primary objective of pharmacologic management of VaD is thus directed at preserving cognitive stability. The two dimensions of VaD pharmacology include [3] prevention of recurrent vascular disease through management of risk factors for cerebrovascular disease and [4] symptomatic treatment of the cognitive and neuropsychiatric symptoms that arise during the course of disease. Figure 7.6 provides a guide to treatment of VCI/VaD.

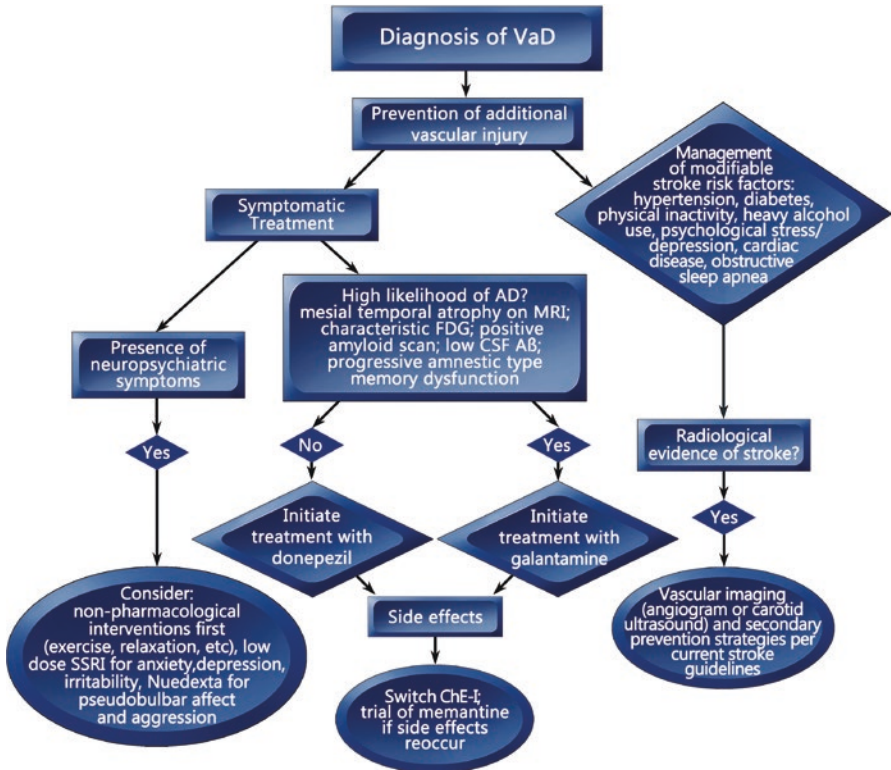


Fig. 7.6 Approach to treatment of VCI/VaD

Risk Factor Management

Because slowing or preventing additional vascular injury is critical to disease course and prognosis in VaD, addressing modifiable risk factors for cerebrovascular disease is the most efficient management strategy for VaD. Patients with VaD should be carefully screened for hypertension, impaired fasting glucose, heavy alcohol or drug use, atrial fibrillation, hyperlipidemia, kidney disease, and obstructive sleep apnea. Table 7.9 lists the modifiable risk factors associated with cerebrovascular disease [44]. Treatment of risk factors should take a measured approach in the elderly as optimal blood pressure and cholesterol targets have not been established in those over 80 years of age. Careful management of blood pressure and glucose

Table 7.9 Modifiable risk factors for stroke [44]

Hypertension
Current smoking
Obesity
Diet
Physical inactivity
Diabetes
Heavy alcohol use
Psychological stress
Depression
Cardiac disease

levels is crucially important, as hypoglycemia and hypotension have been associated with dementia [45] [46]. Although risk factor modification has not been shown to overcome cognitive impairment in VaD, prevention strategies are important for reducing the risk of recurrent stroke [47]. Secondary prevention strategies (platelet anti-aggregants, anti-coagulants, etc) should be recommended as indicated by stroke specific guidelines [47]. Platelet anti-aggregants and antithrombotics are associated with a higher risk of bleeding in patients with cerebral amyloid angiopathy and should be avoided unless there is a compelling indication [48]. There have been few studies of lifestyle changes (healthy diets, smoking cessation, cognitive engagement, and regular exercise) and medical interventions (blood pressure and lipid control) in subjects with established VaD, however, emerging evidence suggests that these strategies may be promising strategies for preventing cognitive decline, especially when initiated in midlife [49]. Healthybrains.org provides guidance for brain healthy lifestyle choices.

Vascular Studies

When cerebral infarction occurs or is identified on neuroimaging, evaluation to define specific subtypes and etiology should be initiated following current guidelines. Evaluation of carotid vessels with ultrasound or vascular imaging should be pursued when vascular lesions are noted in characteristic regions. Cardiac imaging and prolonged heart monitoring should be pursued in patients with multiple infarcts suggestive of a cardioembolic etiology.

Sleep Studies

The effects of obstructive sleep apnea (OSA) on cognitive dysfunction are increasingly recognized [50]. Recently, associations between lower oxygen saturations on polysomnography and microhemorrhages have been reported [51]. Obstructive

sleep apnea is a known risk factor for stroke and death from all causes [52]. All patients being evaluated for VaD should be screened for symptoms suggestive of sleep apnea including snoring, daytime sleepiness, morning headaches, mood changes, witnessed apneas by bed partner, and nocturia. A low threshold of clinical suspicion should prompt further evaluation by a sleep specialist.

Driving Assessment

In light of early deficits in attention, executive, and/or processing speed, a driving history should be obtained from all patients being evaluated for VaD. A history of recent violations or accidents, family members' reports of feeling unsafe, or reckless behavior should be referred for further evaluation. Physical exam or cognitive assessment of significant visuospatial or executive dysfunction should also prompt referral. The American Academy of Neurology has published practice parameters for the evaluation and management of driving risk in dementia [53].

Symptomatic Treatment

Alzheimer's Disease Agents

In clinical studies, cholinesterase inhibitors (ChE-Is) have demonstrated small but significant benefits on cognition in VaD [2]. Because benefits have not been noted in global functioning or activities of daily living they have not been granted regulatory approval for use in VaD. Although many experts argue that the cognitive benefits of these agents seen in clinical trials is likely due to the presence of concurrent AD pathology in VaD cohorts, there is experimental and pathological evidence of cholinergic dysfunction in VaD independent of AD pathology [54]. There is also evidence that ChE-Is improve cerebral blood flow [55], providing an additional rationale for using these agents in VaD. Current guidelines suggests that patients with "pure" VaD may benefit from a trial of donepezil while patients with "mixed" VaD/AD may benefit from a trial of galantamine [4]. Rivastigmine and memantine have also demonstrated benefits on cognition in VaD in smaller, less well-constructed trials. Further study is required to establish whether these agents are beneficial in VaD. Table 7.10 summarizes the current symptomatic therapies for VaD.

Table 7.10 Therapies to improve cognition in VaD

Name	Metabolism	Starting dose (mg)	Therapeutic dose (mg)	Population studied	Benefit seen
Donepezil	Hepatic	5–10	5–10	"pure" VaD	Cognition
Galantamine	Hepatic	8	16–24	"mixed" VaD	Cognition

Psychotropic Agents

Despite a high prevalence of neuropsychiatric symptoms, there is little evidence to guide treatment of these symptoms in VaD populations. Clinical experience and the disability associated with these symptoms suggest that neuropsychiatric symptoms in VaD can be managed using the same cautious approach used in AD (see Chap. 23).

ICD-10 Codes

Vascular dementia without behavioral disturbance F01.50.

Vascular dementia with behavioral disturbance F01.51.

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Chapter 8

Dementia with Lewy Bodies

Kasia Gustaw Rothenberg and James B. Leverenz

Abbreviations

AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ChAT	Choline acetyltransferase
DLB	Dementia with Lewy bodies
NDD	Neurodegenerative disorders
NPI	Neuropsychiatric inventory
NPS	Neuropsychiatric symptoms
PD	Parkinson's disease
PDD	Parkinson's disease dementia
RBD	Rapid eye movement sleep behavior disorder

Clinical Pearls

- Core features of dementia with Lewy bodies (DLB) include fluctuations in cognition with variations in attention and alertness, recurrent visual hallucinations, rapid eye movement sleep behavior disorder (RBD), and parkinsonism.
- Dopaminergic medications are used to address motor aspects of parkinsonism in DLB. Dopaminergic treatment in DLB requires balancing risk of worsened psychosis and potential motor benefit.
- Both the cognitive and behavioral aspects of DLB may respond to acetylcholinesterase inhibitors (AChEIs) and/or memantine.

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- Antipsychotic use in DLB may result in significant worsening of motor symptoms.
- Pimavanserin, a selective-serotonin inverse agonist that preferentially targets 5-HT_{2A} receptors, may be a good therapeutic option for psychosis in the course of DLB.
- Cognitive fluctuations in DLB can last from microseconds observed on EEG to prolonged periods (hours) of reduced arousal.
- DLB and Parkinson's disease dementia (PDD) are distinguished by which symptoms occur first (dementia in DLB; parkinsonism in PDD).

Extent of the Problem, Pathogenesis and Impact

Dementia with Lewy bodies (DLB), a common type of dementia, is underrecognized in clinical practice with patients frequently diagnosed only after many clinician visits and years of symptoms [1, 2]. "Core" features of DLB include fluctuations in cognition with variations in attention and alertness, well-formed and detailed visual hallucinations, parkinsonism as well as REM sleep behavior disorder [3]. Other key "suggestive" features include neuroleptic sensitivity and abnormal dopamine transporter imaging. DLB is also frequently associated with depression, anxiety, delusions, and autonomic dysfunction [4]. There is some debate concerning the frequency of DLB, ranging from as little as 5% of all dementias to the second most common form of dementia after Alzheimer's disease (AD). The term "Lewy body dementia" includes two related disorders characterized by Lewy body pathology, dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). There is extensive clinical overlap between those two conditions and both share the underlying Lewy body pathology. Genetic studies of DLB suggest that this disorder shares risk with both PD and AD [5, 6]. This supports previous research suggesting commonalities of DLB with PD and AD; however, the exact pathobiology of DLB is still being strongly debated [7].

It is difficult even to envision conundrum more complex than DLB. Many different branches of neuroscience try to contribute to understanding of the pathology to be able to develop effective treatments. Numerous studies have linked DLB to significant dysfunction of cholinergic neurotransmission. Activity of choline acetyltransferase, (ChAT, presynaptic cholinergic marker) enzyme, which synthesizes acetylcholine, was found to be low in patients with DLB, particularly in the temporal and parietal cortex. Interestingly in Lewy body cases neocortical ChAT was consistently lower even than in the classical AD cases [8]. Imaging study using AChE positron emission tomography similarly point to more broad and severe cortical cholinergic dysfunction in demented patients with Lewy bodies' pathology as oppose to people who suffered from AD [9]. DLB resembles closer to PD than to AD in its cholinergic neurochemical pathology. Reductions in the biochemical activity of ChAT is generally more extensive in neocortex as opposed to archicortex in DLB and in PD, and muscarinic receptor (postsynaptic cholinergic marker)

binding is significantly increased in DLB and PD [10]. All the above may suggest the possibility of response to pro-cholinergic therapy in patients.

Several studies have reported that abnormalities in glutaminergic neural transmission were associated with Lewy body disorders. An animal model of parkinsonism showed increased glutamate in striatum. NMDA antagonist reduced glutaminergic hyperactivity and restored akinesia and rigidity [11]. In clinical trials glutaminergic receptor antagonists had positive effects on the patients' general status and cognitive functions, severity of fluctuations in mental state, aggression and disinhibition [12–14].

Unlike in primary psychotic disorders, the dopaminergic system may not be the only neurochemical system contributing to hallucinations in DLB. Pathophysiology of psychosis in DLB is most likely multifactorial, where disruption of serotonin and acetylcholine neurotransmissions may play a role [14]. Neuropathologic studies link the development of DLB psychosis with development of Lewy bodies in cortex and amygdala as well as hippocampus [15, 16]. Altered cortical visual processing and rapid eye movement (REM) sleep anomalies have also been proposed as possible contributors to visual hallucinations [17].

Clinical Manifestation

Cognitive Impairment

DLB produces disproportionately severe deficits in visual spatial, attention and executive abilities compared to AD, but relatively less prominent memory deficit [18].

Cognitive Fluctuations

Fluctuating cognition in DLB is a pronounced variation in attention and alertness which can be described as incoherent speech, impaired awareness of surrounding or staring into space for long periods and frequently. The fluctuation may resemble delirium without however identifiable precipitant.

Hallucinations

Recurrent, complex visual hallucinations (VH) continue to be one of the most useful characteristics of a clinical diagnosis of DLB [4]. The visual hallucinations are usually well formed and feature people, children or animals [2]. They tend to occur at night. Auditory and sensory hallucinations have been reported with less frequency along VH.

Parkinsonism

Parallel to fluctuating cognition and visual hallucinations, parkinsonism is a core feature of DLB, however many neurodegenerative disorders are associated with parkinsonism (e.g., Parkinson's disease, progressive supranuclear palsy, frontotemporal dementia and late Alzheimer's disease) [19]. Bilateral symmetric parkinsonian motor symptoms, especially limb rigidity and bradykinesia are common in DLB. Tremor occurs less frequently than in PD, and when present is typically a symmetric postural tremor, rather than an asymmetric rest tremor. Gait may be shuffling with slow turns, and reduced arm swing.

Dysautonomia

Autonomic insufficiency such as: orthostatic hypotension, constipation, urinary incontinence and sialorrhoea have been reported. Autonomic dysfunction occurs due to preganglionic cell loss in the spinal cord and is likely exacerbated by loss of cholinergic neurons.

Sleep

Sleep disorders are quite common with poor sleep efficiency. They include insomnia, early awakening, hypersomnia and REM Sleep Behavior Disorder (RBD). A great deal of attention is being drawn to rapid eye movement sleep behavior disorder (RBD) as an important feature of DLB. RBD is classified as a parasomnia and is characterized by the absence of REM sleep atonia accompanied by dream associated enactment behavior. The presence of RBD is strongly suggestive of a Lewy body disorder, as polysomnographic confirmed RBD has been almost universally associated with Lewy body pathology at autopsy. It significantly influences patient's quality of life and may be complicated by other sleep disorders [11, 20].

Diagnostic Criteria

McKeith and colleagues outlined the clinical and pathological criteria for DLB in 2005 [4]. Recently [3] the DLB consortium has refined its recommendations about the clinical and pathologic diagnosis of the disease. Significant new information has been incorporated about previously reported aspects of DLB, with increased diagnostic weighting given to rapid eye movement (REM) sleep behaviour disorder (RBD) and iodine¹²³ - metaiodobenzylguanidine (MIBG) myocardial scintigraphy. Clinical signs

and symptoms are weighted as either **core** or **supportive**, and biomarkers as **indicative** or **supportive**, based upon their diagnostic specificity and the amount of good quality evidence available. The revised criteria (Table 8.1) continue to generate

Table 8.1 Revised criteria for the clinical diagnosis of probable and possible DLB

Core clinical features
(the first three typically occur early and may persist throughout the course)
<ul style="list-style-type: none"> • Fluctuating cognition with pronounced variations in attention and alertness • Recurrent visual hallucinations that are typically well formed and detailed • REM sleep behavior disorder (RBD) which may precede cognitive decline • One or more spontaneous cardinal feature of parkinsonism—these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, rigidity
Supportive clinical features
<ul style="list-style-type: none"> • Severe sensitivity to antipsychotic agents • Postural instability • Repeated falls • Syncope or other transient episodes of unresponsiveness • Severe autonomic dysfunction e.g. constipation, orthostatic hypotension, urinary incontinence • Hypersomnia • Hyposmia • Hallucinations in other modalities • Systematized delusions • Apathy • Anxiety • Depression
Indicative biomarkers
<ul style="list-style-type: none"> • Reduced dopamine (DaT) uptake in basal ganglia demonstrated by SPECT or PET • Abnormal (low uptake) MIBG myocardia scintigraphy • Polysomnographic confirmation of REM sleep without atonia
Supportive biomarkers
<ul style="list-style-type: none"> • Relative preservation of medial temporal lobe structures on CT/MRI scan • Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity \pm the cingulate island sign on FDG-PET imaging • Prominent posterior slow wave activity on EEG with periodic fluctuations in the pre-alpha/theta range
Probable DLB can be diagnosed if:
(a) two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers or
(b) only one core clinical feature is present, but with one or more indicative biomarkers
Probable DLB should not be diagnosed on the basis of biomarkers alone
Possible DLB can be diagnosed if:
(a) only one core clinical feature of DLB is present, with no indicative biomarker evidence, or
(b) one or more indicative biomarkers is present but there are no core clinical features

(continued)

Table 8.1 (continued)

DLB is less likely:

- (a) in the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation

or

- (b) in the presence of evident as focal neurological signs (other than parkinsonism),

or

- (c) if parkinsonism features are the only core clinical feature and appear for the first time at a stage of severe dementia

DLB should be diagnosed when dementia occurs before, or concurrently with parkinsonism. The term Parkinson's disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson's disease. In a practice setting, the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing one-year rule between the onset of dementia and parkinsonism continues to be recommended

Based on McKeith et al. [3]

categories of **probable** and **possible** DLB [3]. The primary difference in the clinical diagnostic criteria for DLB and PDD is whether the dementia precedes the motor parkinsonism or occurs within a year of onset of parkinsonism (the so-called "1 year rule") [3, 4].

Imaging

A lot of imaging modalities are being studied in DLB. Imaging may provide auxiliary data in the process of clinical diagnosis but the results have to be interpreted cautiously.

MRI (Magnetic Resonance Imaging)

Diffuse grey matter atrophy with relative structural preservation in DLB. Contrary to AD, relative preservation of the medial temporal lobe was adopted as a supportive diagnostic marker for DLB [4]. Marked changes on diffusion imaging in posterior white matter (parieto-occipital) was also reported [21].

Functional Imaging

Occipital hypometabolism and hypoperfusion were one of the first recognized functional imaging features distinguishing DLB from AD, which is a supportive but not specific feature. Both AD and DLB show diminished temporal-parietal hypometabolism.

FDG-PET (Fluorodeoxyglucose Positron Emission Tomography)

Preservation of the posterior cingulate metabolism relative to the cuneus and precuneus “Posterior Cingulate Island Sign”, with relatively preserved mesial temporal lobe activity is seen in DLB and not AD [22].

DAT-Scan

Presynaptic dopaminergic nerve terminal imaging shows diminished activity in putamen and caudate but does not differentiate DLB from other Parkinsonian syndromes (see DAT-Scan in chapter on Parkinson’s disease).

Amyloid-PET Imaging

Greater amyloid deposition compared to healthy or Parkinson’s patients but less than AD patients.

MIBG Myocardial Scintigraphy

Metaiodobenzylguanidine (MIBG) uptake is assessed using the ratio of the heart to the upper mediastinum (H/M ratio). The H/M ratio was significantly lower in patients with DLB than in controls and AD patients [23]. This lower uptake suggests myocardial postganglionic denervation in DLB patients irrespective of parkinsonian features.

Treatment

Pharmacotherapy of DLB is as complex as its clinical phenotype and pathobiology and currently is exclusively symptomatic. At this time, no medication is approved by the US FDA for the treatment of DLB. Worldwide only donepezil is approved for treatment of DLB in Japan [24]. Figure 8.1 discusses treatment for patients diagnosed with DLB.

Management of Motor Symptoms

In practice dopaminergic medication are used to address motor parkinsonism in DLB. Dopaminergic therapies however can lead to an increase in visual hallucinations and do not appear to be as effective in addressing motor symptoms as observed in PD [25, 26]. Thus, in the context of DLB, dopaminergic agonists should be avoided and carbidopa/levodopa therapeutic trials should proceed with caution.

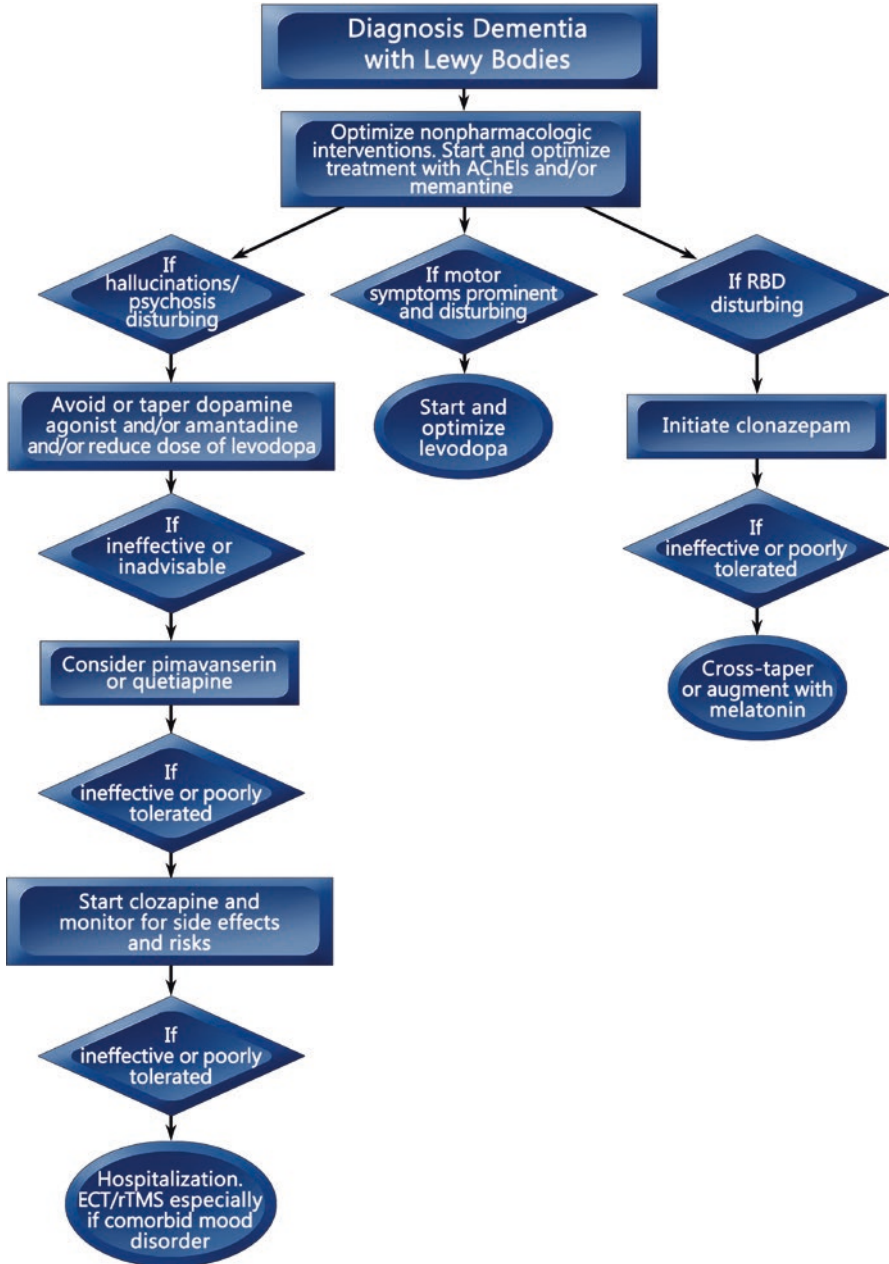


Fig. 8.1 Treatment of DLB

Management of Cognitive Symptoms

The cognitive and behavioral aspects of DLB respond to acetylcholinesterase inhibitors [27]. Moreover, data from controlled trials are available to support the use of AChEIs in DLB. Donepezil demonstrated significant cognitive, behavioral, and global improvements in DLB patients, reducing caregiver burden at the highest dose [28, 29]. Donepezil was demonstrated to be generally safe and well tolerated, which resulted in its registration for the treatment of DLB in Japan [24]. Rivastigmine has also demonstrated both cognitive and behavioral benefits [30]. Meta-analyses support the use of donepezil and rivastigmine to address cognition, hallucinations, delusions, and to improve activities of daily living (without worsening motor symptoms of parkinsonism) [28, 30]. Evidence for galantamine, although limited, suggest benefits for psychiatric symptoms and cognition in DLB patients [31].

Memantine, although with a favorable pharmacological profile, may be less beneficial in DLB. In practice memantine appears to be well tolerated, but provides few benefits to patients [13]. Consistent with previous meta-analyses, memantine was superior to placebo only in terms of clinician impression of change when analyzed as a continuous outcome measure; this advantage was not observed when analyzed as categorical data in terms of improvement or absence of deterioration. Secondary analyses suggest some, but very limited advantages of memantine over placebo in relation to aspects of attention, sleep, caregiver burden, some aspects of quality of life [11, 12].

Management of Neuropsychiatric Symptoms

Another difficulty comes with management of psychosis of DLB. Antipsychotics utilized for hallucinations often cause serious side effects, such as increasing parkinsonism, sedation, and cognitive impairment, and are associated with an increased risk for mortality. They are often used off label and, even if effective, they should not be used indefinitely [27]. Consensus opinion suggests use of atypical antipsychotics, such as quetiapine and clozapine in this patient population [4]. Before considering a trial of antipsychotic therapy, consideration should be made for severity (i.e., is the psychosis sufficiently severe to require pharmacotherapy) and whether modification of other medications (e.g. dopaminergic agents) may assist with management of these symptoms.

Theoretically, AChEIs should be beneficial in managing hallucinations in DLB. Neurochemical analyses of temporal cortex has revealed a distinction between hallucinating and non-hallucinating patients in both cholinergic and monoaminergic transmitter activities. In contrast with ChAT, which was more extensively reduced in hallucinating individuals, serotonergic receptor binding, dopamine and serotonin metabolites were significantly decreased in non-hallucinating cases. These results suggest that an imbalance between monoaminergic and cholinergic transmitters is

involved in hallucinogenesis in DLB [14]. Clinical trials are consistent with this neurochemical hypothesis. Donepezil [32] as well as rivastigmine [33] may be effective in reducing visual hallucinations in DLB. Of note, patients have had a common side effect of nightmares from taking cholinesterase inhibitors at bedtime. The latter side effect can usually be easily resolved by switching the dosing to the morning.

Visual hallucinations, however, seem to be resistant to AChEIs in a significant number of patients who may require the trial of antipsychotics. Unfortunately efforts to treat DLB with antipsychotics, have been marginally successful and associated with significant deterioration of the motor symptoms [34]. Typical antipsychotics, especially potent blockers of dopaminergic receptors, are in general contraindicated in DLB. Novel atypical antipsychotics, those with a more favorable mechanism of action (less dopaminergic impact), seem to be of limited efficacy in managing psychosis in DLB. Olanzapine effectiveness in reducing psychiatric symptoms appears to be limited [35] and risperidone does not appear to be beneficial [34]. While quetiapine is probably the most common antipsychotic agent used for controlling disturbing visual hallucinations or delusions in patients with DLB, there are no definitive randomized control trials clearly supporting its effectiveness [36, 37]. Clozapine has been proven efficacious in the treatment of PD psychosis in randomized controlled trials even in very small doses (6.25–50 mg daily) and even for medication-induced psychosis [38, 39]. Clozapine was proved to be effective in PDD based on a chart review study but with prominent side effects like drooling, sedation, tremors, constipation, and delirium [40]. To date no studies of clozapine for DLB have been published, so its efficacy is being presumed by extrapolation of results from PD and PDD studies [41]. Nevertheless, the risk of agranulocytosis and the necessity of blood monitoring with clozapine have led many experts to recommend a trial of other atypical antipsychotics before attempting clozapine therapy [40, 41].

Citalopram, amantadine and selegiline were not proved beneficial in studies so far. There is weak evidence for potential efficacy of armodafinil/modafinil, levodopa, zonisamide, ramelteon, clonazepam, gabapentin, rotigotine, duloxetine, escitalopram, trazodone [12]. There is lack of randomized placebo controlled studies with those pharmaceuticals to recommend for or against use of them in DLB.

In cases of severe, treatment resistant psychosis, especially comorbid with mood disorders hospitalization should be considered. Severe pharmacotherapy resistant DLB patients may benefit from somatotherapy like Electroconvulsive Therapy or Transcranial Magnetic Stimulation [42].

Treatment options are expanding with the introduction of psychopharmaceuticals with a new mechanism of action. Pimavanserin is a selective-serotonin inverse agonist of 5-HT_{2A} receptors. It doesn't bind to dopaminergic receptors. In Parkinson's disease, treatment with pimavanserin resulted in fewer and less severe hallucinations and delusions without worsening parkinsonism [43]. Pimavanserin, and similar compounds in development, may soon be considered the standard of pharmacotherapy of psychosis in PD. Pimavanserin may be as well beneficial in DLB cases, although the clinical evidence of such an effect has yet to be established.

Management of Sleep Disorders

Besides psychosis, sleep disorders and especially REM sleep behavior disorder (RBD) pose a challenge in the treatment of DLB. RBD may require intervention due to its detrimental influence on patients and their bed partners. Clonazepam has been the drug of choice in those without significant cognitive impairment. Clonazepam is usually effective at 0.25–0.5 mg/night, but doses above 1 mg nightly are necessary in some cases [2, 20]. Clonazepam, however as a long acting benzodiazepine is notorious of causing somnolence, cognitive impairment, and may worsen other sleep disorders such as obstructive sleep apnea. Additionally, residual RBD symptoms are commonly observed, despite treatment. Melatonin has been shown to have some effectiveness in RBD, and has a better side effects profile to clonazepam. Significant improvements in Clinical Global Impression scores and a reduction in REM sleep without atonia were noted using 3 mg of melatonin for 4 weeks in one study [44] however, in clinical practice melatonin is often used in doses up to 12 mg for RBD [20, 45]. Recent experience with melatonin supports its use for RBD in a doses range 3–12 mg/night as sole therapy, or in conjunction with clonazepam when either melatonin or clonazepam alone is ineffective [20]. Given the lower side effect profile, clinicians may want to use a trial of melatonin first before using clonazepam. Memantine and acetylcholinesterase inhibitors have been reported to improve RBD in some cases, but no clinical trials have been reported to date. Other more effective alternative or adjunctive interventions are needed for better clinical management of RBD with melatonin and melatonin receptor agonists [20, 45].

Hypersomnia is also common in patients with DLB as a consequence of combination of different processes. In DLB there is obvious nocturnal sleep fragmentation, which may be accompanied by sleep apnea, periodic limb movements all resulting in alterations of sleep–wake cycle. Treatment of obstructive sleep apnea and management of periodic limb movements should be considered. Wake-promoting drugs such as modafinil can be used for hypersomnia, but they have not been tested in randomized controlled trials [2, 20].

While there are a number of symptomatic therapies for DLB, development of additional therapies for DLB are critically needed to improve our ability to treat the range of cognitive, motor, sleep, autonomic, and behavioral symptoms observed in the complex neurodegenerative disorder.

ICD-10 Codes

G31.83 Possible or Probable Major Neurocognitive Disorder with Lewy bodies

F02.80 without behavioral disturbance

F02.81 with behavioral disturbance.

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Chapter 9

Frontotemporal Dementia

Gabriel C. Léger

Clinical Pearls

- Although considered a “young-onset” dementia, FTD can occur at later ages, with approximately 25% of patients occurring after age 65.
- The early accurate diagnosis of bvFTD depends on a detailed history of significant behavioral changes representing a departure from the premorbid state. Neuropsychological assessment and imaging alone are not sufficient for a diagnosis.
- Motor changes can emerge as FTD progresses, but can also be present at the time of diagnosis. These take the form of Parkinsonism (PSP and CBD—usually associated with tau pathology) or motor neuron disease (MND or ALS—invariably associated with TDP-43 pathology).
- Isolated progressive language deficits must be present for at least 1 or 2 years for PPA to be diagnosed. These language deficits must remain the principle cause of disability as the disease progresses.
- FTD is a highly genetic syndrome, with up to 50% of patients showing a strong familial inheritance. Many genes have been identified, but MAPT, C9orf72, and GRN account for most familial cases.
- The underlying pathology in FTD is complex. Although any one case will generally be the consequence of a single pathology, FTD remains a syndrome that results from many possible processes, the two most common being tau and TDP-43.
- There are no specific treatments for FTD or PPA. Unless Alzheimer’s disease pathology is highly suspected (as in lvPPA), there is no role for cholinesterase inhibitors or memantine, which may worsen the clinical symptoms. Serotonergic agents are the treatment of choice for behavioral changes. Non-pharmacologic management such as the “ABC” approach may be useful.

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Introduction—Nomenclature, Epidemiology, Genetics, and Pathology

Frontotemporal dementia (FTD) is a term used to express a collection of possible clinical presentations that develop as the consequence of one of a number of distinct pathological processes. Frontotemporal Lobar Degeneration (FTLD) is a pathological term that refers to the fairly selective degeneration of the frontal and anterior temporal lobes and results in the clinical manifestations of FTD [1]. Although these clinical manifestations are fairly consistent, the underlying pathological processes can be varied.

Reflecting its focal onset, FTD presents classically as a progressive degenerative disorder involving the initially selective disintegration of either behavior (behavioral variant FTD or bv-FTD) or language (primary progressive aphasia—PPA). PPA generally evolves from one of three different patterns of speech dysfunction: semantic dementia (or semantic variant, sv-PPA), non-fluent or agrammatic variant (nfv-PPA) and the logopenic variant (lv-PPA). Behavioral variants account for nearly 60% of cases while PPA accounts for 40% [2]. There is also significant overlap with movement disorders (progressive supranuclear palsy and corticobasal degeneration—PSP and CBD) and motor neuron disease or amyotrophic lateral sclerosis (MND/ALS). Patients may initially present with a defined clinical syndrome, such as nfv-PPA, and then evolve to develop features of CBD, PSP, or even MND [3, 4]. Some have recommended the use of “overlap” terms such as PPA-CBD to better reflect this evolution [5].

Although often a “young-onset” dementia, accounting for nearly half of dementias occurring before age 65 [6], FTD also affects older patients. One quarter of patients with FTD present after age 65, often being misdiagnosed as AD [7]. Younger onset patients are often misdiagnosed with psychiatric disorders, including depression, obsessive compulsive disorder (OCD), bipolar disorder, and even schizophrenia [8]. The reported prevalence of FTD varies, but is estimated at 15–22/100,000 [7]. Average age of presentation is in the sixth decade. There may be a slight overrepresentation of male patients.

FTD is a highly heritable disease. As many as 50% of cases report a family history with approximately 15% showing a clear autosomal dominant pattern of inheritance [9], with most familial cases explained by one of three common mutations (Microtubule Associated Protein Tau—MAPT, progranulin—GRN, and Chromosome 9 open reading frame 72—C9orf72). Together, these three mutations account for up to 20% of all cases of FTD.

Unlike Alzheimer’s disease, in which diagnostic pathological changes must include the combined presence of both amyloid-based plaques and tau-based neurofibrillary tangles, pathologic changes in FTLD can be varied. Two different abnormal inclusions each account for about 45% of cases. These are accumulations of either abnormal tau or TDP-43. The remaining 10% of cases include FUS based pathology (FUsed in Sarcoma) or other yet to be characterized changes. Pathologic MAPT mutations always lead to tau pathology, while mutations in GRN and C9orf72 result in TDP-43 related changes. Clinically, cases that progress to include movement disorders tend to be the consequence of tau changes, while the development of motor neuron disease is almost exclusively the result of TDP-43 pathology.

Although frequently used interchangeably, Pick's disease (PiD) is currently considered a subgroup of the FTLDs. It is pathologically defined by the presence of circumscribed frontotemporal atrophy and associated tau containing intraneuronal agyrophilic spherical aggregations called Pick bodies.

Clinical Manifestations, Radiologic Findings, and Diagnostic Criteria

Patients with FTD present with insidious changes involving either behavior (bvFTD) and/or language (PPA) and the core diagnostic criteria reflect this dichotomy [10, 11].

Behavioral Variant FTD (bvFTD)

The primary manifestations of bvFTD involve early progressive changes in socio-emotional behavior or comportment, and include (1) behavioral disinhibition, (2) apathy and inertia, (3) loss of sympathy or empathy, (4) perseverative, stereotyped or compulsive/ritualistic behaviors, and (5) hyperorality and dietary changes. (6) Cognitive changes may also be present and involve executive/generation deficits with relative preservation of memory and visual spatial abilities.

Apathy and inertia are possibly the earliest and most common manifestations and can present as subtle changes such as difficulties making decisions, increased passivity, and reduced interest in usual hobbies. Progression often leads to more significant and impactful changes such as reduced attention to (or care about) work and home responsibilities, and personal hygiene. Early loss of functional independence is not uncommon, despite relative preservation of cognition.

Disinhibition may be less common than apathy, but is often more disruptive. Socially inappropriate behaviors and loss of decorum or manners are embarrassing to family and include excessive familiarity, inappropriate touching or hugging of strangers, or loud rude unconsidered remarks (such as about people's weight or appearance). Disinhibition can also take the form of impulsivity and lead to rash or careless actions. Criminal behavior, including speeding, theft (i.e., shoplifting), public nudity or urination, and even assault, can occur.

Loss of empathy usually manifests as reduced personal warmth and affection towards loved ones. There is often inability to properly appreciate or respond to others' needs or emotions. This may manifest as striking selfishness or lack of concern for a loved ones' illness or tragedy.

Compulsive, repetitive, or ritualistic behaviors can take on various forms. There can be repetitive stereotyped behaviors such as incessant humming, rocking, or tapping. Verbal stereotypies may include repetition of words or catch phrases. Obsessive cleaning and insistence on rigid orderliness can occur. Other complex behaviors may involve hoarding, repetitive trips to the bathroom, or rigid and ritualistic feeding habits (such as eating only certain foods at certain times).

Dietary changes may include excessive sometimes compulsive binge eating (even in the face of satiety), new food preferences (most often for carbohydrates) or rigid or ritualistic food fads. There may be disregard for the poor comestible nature of the food in question (eating discarded foods from the garbage). There may even be consumption of inedible objects such as buttons or coins. Weight gain is common and is a relatively unique feature of FTD.

Early cognitive changes are usually subtle and may not be detectable with routine bedside diagnostic testing. Neuropsychological testing may capture deficits in attention and executive functions: working memory, cognitive flexibility and control (set-shifting), generation (lexical fluency), and abstraction. Performance in other cognitive domains, in particular episodic memory and visual spatial functions is generally spared, although there are documented exceptions. Experimental tasks that probe Theory of Mind or social cognition may turn out to be most sensitive to early changes, but their development has not yet reached widespread clinical use. Failure on any task may be more the consequence of rule-breaking or poor effort than from an actual cognitive deficit.

Additional manifestations of the disease not captured by the diagnostic criteria can include psychosis, mood disorder, or OCD. Coupled with the relative initial mildness and frequent delayed appearance of cognitive deficits, as well as the younger age of onset, these changes often lead to psychiatric misdiagnosis for as many as 50% of patients [12]. This results in diagnostic and effective treatment delays.

Another critical finding in patients with bvFTD is the early presence of profound anosodiaphoria (awareness of a deficit but absence of adequate concern about its importance or impact) or anosognosia (lack of awareness altogether).

Physical examination in bvFTD is usually normal. As the disease evolves, patients may begin to show signs of asymmetric or axial extrapyramidal involvement, apraxia, eye movement abnormalities, and early falls, heralding a clinical trajectory towards CBD or PSP, or upper and lower motorneuron disease (weakness, spasticity, and fasciculations), betraying the development of FTD-ALS. These disorders are discussed elsewhere in this book. Occasionally, ALS or CBD/PSP disorders can be the initial manifestations of an FTLT-based pathology, and behavioral or language changes appear later in the course of the disease.

Radiological Findings

Using the Rascovsky criteria, the presence of characteristic findings on brain imaging raise the diagnostic confidence of bvFTD from possible to probable (Figs. 9.1 and 9.2). These include early and isolated, often circumscribed frontal and/or anterior temporal atrophy on magnetic resonance imaging (MRI) or computerized tomography (CT), or hypoperfusion or hypometabolism in the same areas on single photon emission computed tomography (SPECT) or fluorodeoxyglucose positron emission tomography (FDG) PET scan. For bvFTD, right-sided predominance of abnormalities is more frequent. SPECT or PET finding may precede the development of MRI changes by a few years. Absence of atrophy on MRI does not exclude the diagnosis. Conversely, the presence of such atrophy should never lead to a diagnosis in the absence of the clinical syndrome.

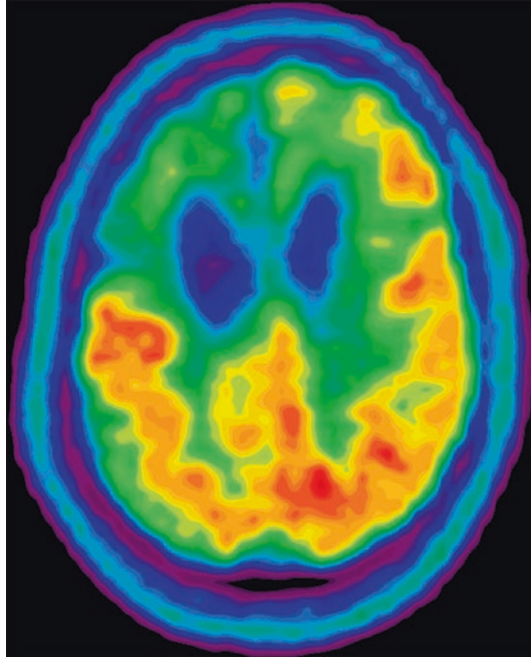


Fig. 9.1 FDG-PET (*axial view*). Note profound hypometabolism involving anterior right frontal mesial, polar, and convexity

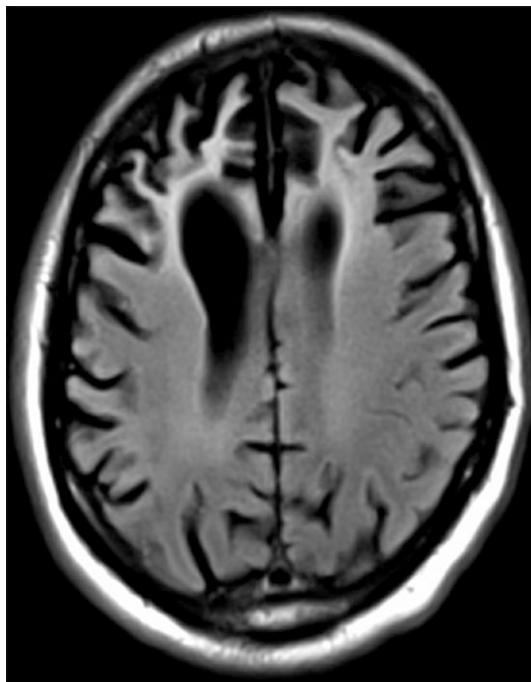


Fig. 9.2 FLAIR-MRI (*axial view*). Note knife-like cortical atrophy of frontal areas

New imaging techniques such as resting state functional MRI (fMRI) may reveal very early disintegration of key networks involving the anterior cingulate and fronto-insular cortices. Further development will be required before these can be applied clinically.

Each group of behavioral changes described above have been attributed to pathologic involvement of specific brain areas or disruption of networks involving: (1) anterior cingulate for apathy, (2) right orbitofrontal for disinhibition, (3) right fronto-insular and anterior temporal for loss of empathy, (4) lateral temporal and basal ganglia for compulsive behaviors, and (5) right orbitofrontal and insular cortices, and ventral striatum and hypothalamus for dietary or appetitive changes. The presence of specific behavioral changes and matching atrophy patterns on brain imaging (MRI or PET) help bolster diagnostic confidence.

Diagnosis of bvFTD

The diagnosis of *possible* bvFTD requires the clinician to elicit at least three of the six core behavioral (5) and cognitive (1) criteria described above (Table 9.1 and “Diagnostic flowchart for bvFTD”; Fig. 9.3). Because of the presence of early anosognosia, a detailed interview with a reliable caregiver or life partner is usually necessary. Although many of the relevant changes are sometimes spontaneously volunteered, directed questioning with examples as described above are often required. Neuropsychological testing may be required to capture the presence of early executive dysfunction. In moderately advanced cases, bedside cognitive testing (such as a Montreal Cognitive Assessment [MoCA]) may be adequate. Patients with early disease may not initially meet three criteria and reassessment in 6–12 months may be required. The diagnosis becomes *probable* when corresponding imaging abnormalities are found on MRI/CT or PET/SPECT *and* there is clear functional decline. The Rascovsky criteria have been found to be 85–95% sensitive and 82% specific for a diagnosis of possible bvFTD and 75–85% sensitive and 95% specific for probable bvFTD [10, 13]. Interrater reliability is also very high at 0.81 and 0.82 for possible and probable disease [14]. The presence of a pathologic mutation or confirmation (biopsy or post-mortem) of histopathologic changes raise the level diagnostic certainty to one of “*definite*”.

The presence of any non-degenerative neurological, medical, or psychiatric disorder that better accounts for the behavioral changes should preclude a diagnosis of bvFTD. The presence of biomarkers that strongly support other neurodegenerative diseases (AD, Lewy body diseases, vascular disease) is allowed in “possible” bvFTD, but would exclude a “probable” diagnosis.

Primary Progressive Aphasia (PPA)

There are three variants of PPA: nonfluent/agrammatic (nfv), semantic (sv), and logopenic (lv) [11, 15]. While the histological changes underlying semantic and nonfluent variants are most often consistent with FTL, the logopenic variant is

Table 9.1 Diagnostic criteria for FTD

Syndrome	Possible/clinical diagnosis	Probable/imaging supported diagnosis	Exclusionary criteria
bvFTD	<p>At least three of the following:</p> <ul style="list-style-type: none"> • Early behavioral disinhibition • Early apathy or inertia • Early lack of empathy or sympathy • Early perseverations, stereotypies or compulsions • Dietary habit changes or hyperorality • Executive-predominant deficits on neuropsychological testing with relative sparing of memory and visuospatial skills 	<p>All three of the following:</p> <ul style="list-style-type: none"> • Meets possible criteria • Significant decline per informant, or CDR, or FAQ • Imaging consistent with bvFTD (frontal and/or anterotemporal) 	<ul style="list-style-type: none"> • Deficits are better explained by alternative diagnosis (degenerative, nondegenerative, or psychiatric) • Biomarkers strongly indicative of Alzheimer’s disease or other neurodegenerative process (required for diagnosis of probable bvFTD) • Deficits are better explained by alternative diagnosis (nondegenerative, or psychiatric) • Prominent initial memory, visuospatial, or behavioral deficits
nvfPPA	<p>At least one of the following:</p> <ul style="list-style-type: none"> • Agrammatism • Effortful, halting speech with inconsistent sound errors (AOS) <p>At least two of the following:</p> <ul style="list-style-type: none"> • Impaired comprehension of syntactically complex sentences • Spared single-word comprehension • Spared object knowledge 	<p>Both of the following:</p> <ul style="list-style-type: none"> • Meets possible/clinical criteria • Imaging consistent with nvfPPA (left posterior frontoinsular) 	
svPPA	<p>All of the following:</p> <ul style="list-style-type: none"> • Impaired confrontation naming • Impaired single-word comprehension <p>At least three of the following:</p> <ul style="list-style-type: none"> • Impaired object knowledge • Surface dyslexia or dysgraphia • Spared repetition • Spared grammar and motor speech production 	<p>Both of the following:</p> <ul style="list-style-type: none"> • Meets possible/clinical criteria • Imaging consistent with svPPA (anterior temporal) 	
lvPPA	<p>All of the following:</p> <ul style="list-style-type: none"> • Impaired single-word retrieval in spontaneous speech and naming • Impaired repetition of sentences and phrases <p>At least three of the following:</p> <ul style="list-style-type: none"> • Phonologic errors in spontaneous speech and naming • Spared single-word comprehension and object knowledge • Spared motor speech • Absence of frank agrammatism 	<p>Both of the following:</p> <ul style="list-style-type: none"> • Clinical diagnosis of logopenic variant PPA • Imaging consistent with lvPPA (predominant left posterior perisylvian or parietal) 	

Based on [10, 11]

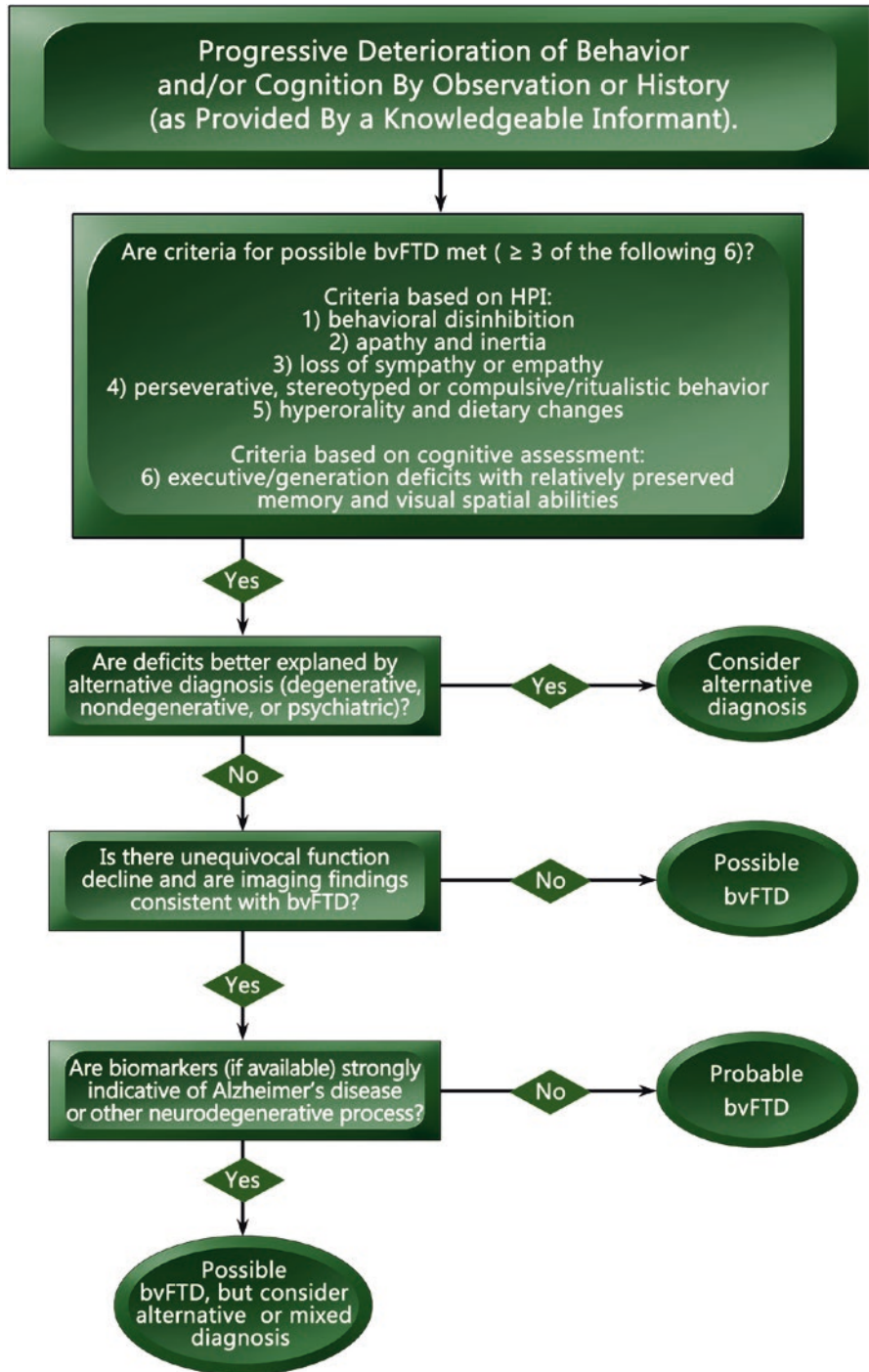


Fig. 9.3 Diagnostic flowchart for bvFTD

more frequently (although not exclusively) the consequence of Alzheimer’s disease pathology. The 2011 Gorno-Tempini criteria allow for the classification of most progressive aphasias, but some patients may fail to meet criteria for any, or meet them for more than one, leading to terms such as “mixed” PPA (PPA-M) [16] or “not otherwise specified” (PPA-NOS) [5]. Closely related to *nfv*-PPA, primary progressive apraxia or speech (PPAoS) has been described and is characterized by impaired articulation and production as a consequence of a breakdown in motor programming, with a general sparing of language, at least initially [17].

Diagnosis of PPA is a two-step process. Before subtyping, patients must first meet basic PPA criteria as defined by Mesulam [11, 18, 19]: there must be (A) an insidious isolated decline in language, affecting at least one of speech production, object naming, syntax, or word comprehension, and (B) the aphasia must be the most prominent deficit for at least the initial 1–2 years and remain the principle cause of any impairment in activities of daily living (ADLs) (see “Diagnostic flow chart for PPA”; Fig. 9.4).

Further characterization of the aphasia can normally be accomplished by examining the main language domains, through simple observation and specific tasks. These domains include speech production (grammar, motor speech, sound errors, and word finding pauses), repetition (both short and longer sentences), single-word and syntax comprehension, confrontational naming, semantic knowledge, and reading/spelling [11]. See Table 9.1 for diagnostic criteria. See also “Approach to the clinical evaluation of a speech disorder” and to Table 9.2 for examples of tests and criteria specific findings. See the “Simplified flowchart for the diagnosis of PPA” for a streamlined approach based on the most critical diagnostic findings (Fig. 9.5).

As with *bv*FTD, there are levels of confidence in the diagnosis: clinical, “imaging-supported”, and pathologic. Clinical diagnosis depends on the classification of the patient’s deficits according to the clinical criteria explored below. Once clinical criteria are met, imaging-supported criteria are considered. Because there is generally a direct correspondence between language symptoms and the site of anatomic damage, there must be structural or functional imaging changes in a distribution consistent with the clinical syndrome. A particular genetic mutation or specific pathology defines the disorder as FTL spectrum, AD, or some other known disease entity. Unfortunately, pathologic diagnoses do not further enhance characterization of the clinical syndrome as there is significant overlap between clinical presentations and possible underlying pathologies. Mixed pathologies are also not uncommon in older patients.

Nonfluent Variant PPA (nfvPPA)

*Nfv*PPA is characterized by early difficulties in motor speech output and loss of syntax (Table 9.1). Speech is effortful (slow and labored), with frequent pauses and grammatical errors. Utterances are generally short and simple, with omission of function words and inflections. There may be articulatory deficits with inconsistent speech sound errors, including distortions, deletions, substitutions, insertions, or transpositions of speech sounds. Prosody is usually also affected. Patients are often aware of, and

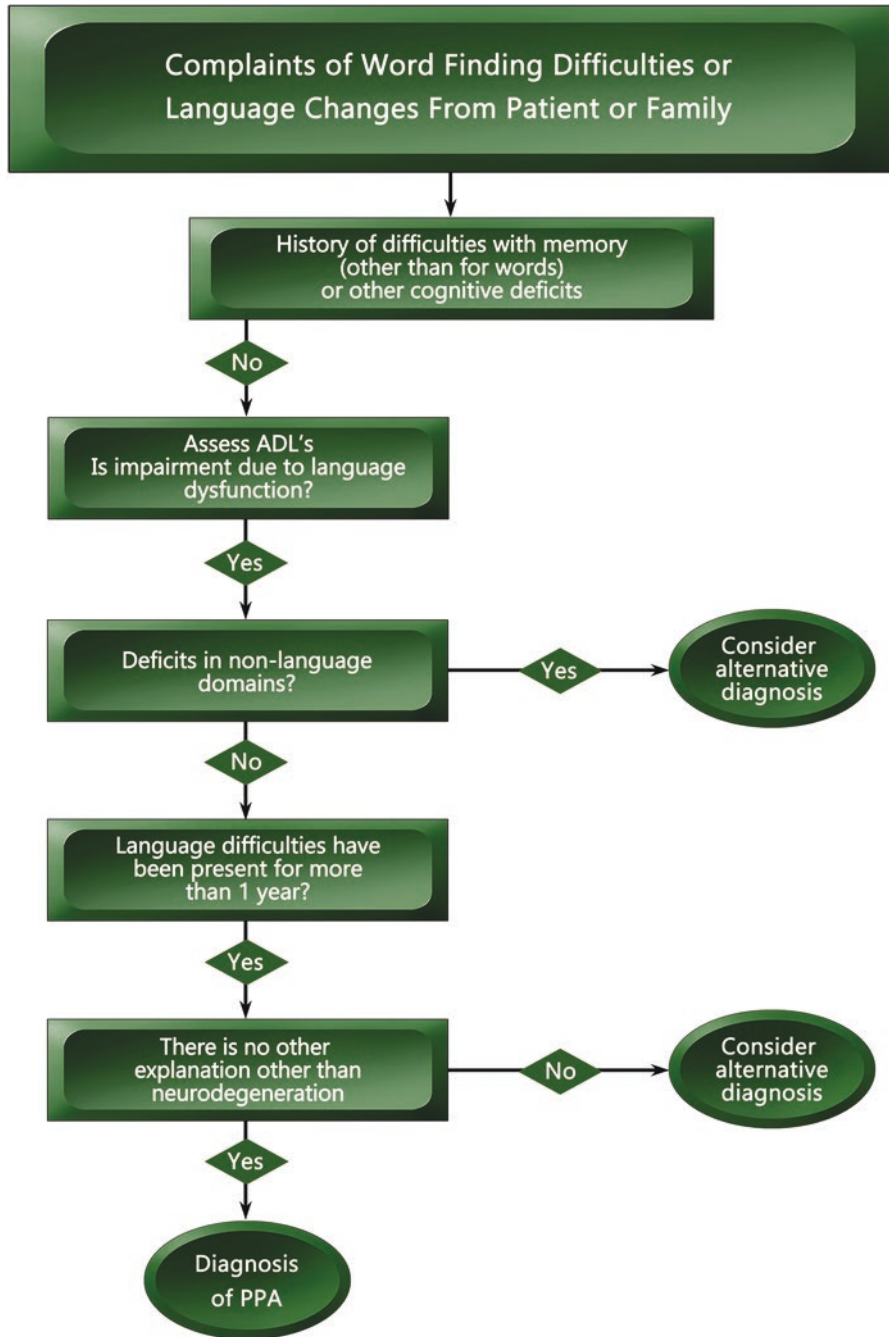


Fig. 9.4 Diagnostic flowchart for PPA

Table 9.2 PPA diagnostic criteria-specific tests and findings

Speech/ language function	Select example of tasks	Look for	Most impaired in
Speech production			
Grammar	Spontaneous speech Picture description task	Grammatical structure Mean length of utterance Speech rate Accuracy of content Melody & Prosody Error types in word selection Articulation	nfvPPA
Motor speech	Repetitions of multisyllabic words Diadochokinesis of speech articulators Spontaneous speech	Effortfulness & Hesitations Presence of apraxia of speech or dysarthria Speech sound errors Factors that affect articulation (e.g., word length in syllables)	nfvPPA
Confrontation naming	Single-word retrieval in response to pictures, sounds, foods, and odors	Error rate Delay in naming Factors that affect accuracy (e.g., familiar vs. unfamiliar items, nouns vs. verbs, semantic category) Error types (e.g., semantic vs. phonemic errors)	Severe in svPPA with semantic errors Moderate in lvPPA with phonemic errors
Repetition	Repetition of words, phrases, and sentences	Factors that affect accuracy (e.g. predictability of the phrase, sentence length, grammatical complexity) Error types (phonologic vs. articulatory)	lvPPA with phonological errors
Single-word comprehension	Word-to-picture matching Word-to-definition matching Synonym matching	Factors that affect comprehension (e.g., familiarity, frequency, grammatical word class)	svPPA
Sentence comprehension	Matching orally presented sentences to pictures Answering yes/no questions Following directions	Factors that affect comprehension (e.g., grammatical complexity; reversibility of the sentence, e.g., The boy was kicked by the girl vs. The ball was kicked by the girl)	nfvPPA when effect of grammatical complexity lvPPA when length and frequency effect
Semantic knowledge	Picture-picture matching Odd-one-out Semantic associations Gesture-object matching Sound-picture matching	Factors that affect object knowledge (e.g., familiarity, semantic category)	svPPA

(continued)

Table 9.2 (continued)

Speech/ language function	Select example of tasks	Look for	Most impaired in
Reading/ spelling	Regular and irregular word lists	Factors that affect reading/ spelling accuracy (e.g., regularity, frequency, word class) Error types (e.g., regularization, phonologically plausible errors; articulatory distortions)	svPPA with “regularization” errors lvPPA with phonologic errors

Based on [11]

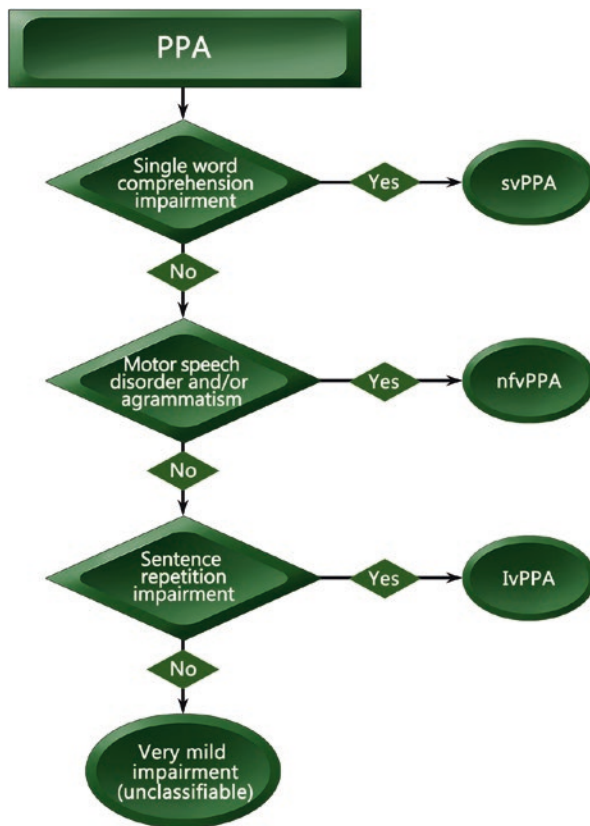


Fig. 9.5 Simplified flowchart for diagnosis of PPA variants

frustrated by, these deficits. Spared are single-word comprehension and object knowledge. There may be deficits in comprehension of grammatically complex sentences.

In some patients, very mild apraxia or slowing of fine finger movements may be present. These findings are harbingers as progression predominantly involves the development of motor changes consistent with CBD or PSP.

MRI shows focal atrophy and FDG-PET reveals focal hypometabolism involving left posterior frontal and insular regions (Figs. 9.6 and 9.7). The most frequent histopathology is tau, with less frequent cases involving TDP-43. Well characterized nfvPPA is almost never the consequence of AD pathology.

Semantic Variant PPA (svPPA)

Previously labeled *Semantic Dementia*, this clinical syndrome is characterized by the presence of *anomia* and *single-word comprehension deficits* (Table 9.1). These represent core features and both must be present for the diagnosis. Anomia is not uncommon in many neurodegenerative conditions, but it tends to be severe in

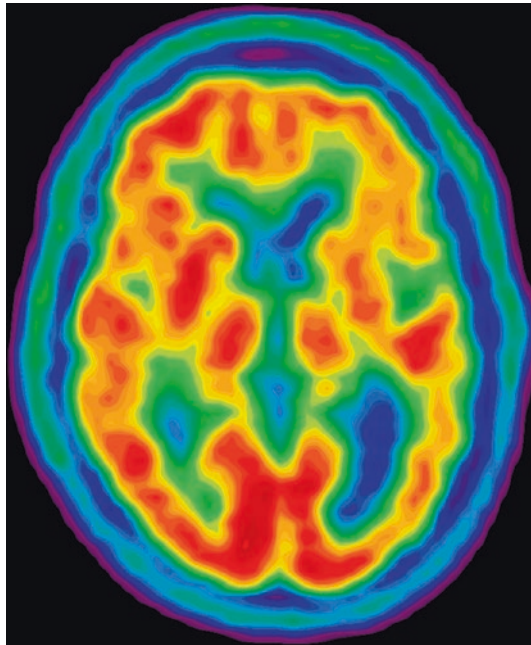


Fig. 9.6 FDG-PET (*axial view*). Note subtle hypometabolism involving left anterior perisylvian (frontal opercular) areas

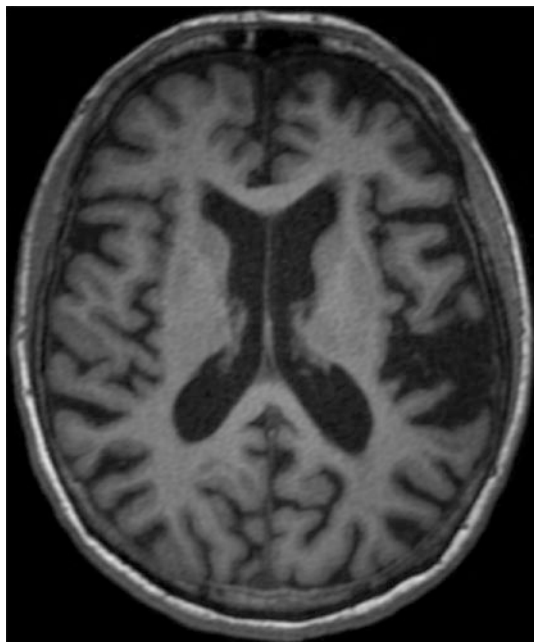


Fig. 9.7 T1-MRI (*axial view*). Note extensive atrophy of anterior perisylvian areas on the left relative to the right

svPPA, in which additional information about the object in question (“object knowledge”, a form of semantic knowledge) may also be missing. A pen, for instance, is held in the dominant hand in a particular way and is used for writing. This kind of information may be completely lost, especially for less common (low-frequency) words—contrast for instance the less common word “zebra” with the more common or familiar “cat”.

Single-word comprehension deficits arise when the patient cannot recognize, describe, or define an object or idea. It is also the consequence of loss of object knowledge. When asked to draw a clock, patients with moderately severe svPPA may simply say: “Clock? What’s a clock?”. They will be unable to name a clock when shown a picture or a cartoon of one, know that clocks are used to tell time, or recognize “*tic-toc*” as the sound that a clock may produce. As suggested by the eventual inability to recognize the sound “*tic-toc*”, deficits in object recognition and knowledge can be multimodal. Recognition failure will ultimately transcend all sensory modalities such that the tactile experience of a rose petal or thorn, or the scent of its flower, will not be of any additional benefit in identifying a rose bush.

Early deficits in naming and word comprehension usually involve low-frequency words, but with progression, the meaning and semantic knowledge of more com-

mon words will also be lost. Selective involvement of certain object categories (tools, animals, people, or concrete vs. abstract) may be present early, but all are involved, eventually.

Another consequence of loss of object or word knowledge is the inability to recognize words with irregular spelling or pronunciation (*e.g.* “yacht”, “colonel”, and “cellist”). This results in so-called *surface dyslexia* and *dysgraphia*, where the patient will “regularize” such words when read or written: the word colonel would be read as “kol-o-nel” and written in some form to sound like “kur-nl”.

Typically, even in advanced disease, repetition and motor speech remain intact. Adequate grammar, albeit with a shrinking vocabulary pool, is generally retained.

Even in the earliest stages, PET and MRI show focal hypometabolism or atrophy in the lateral and ventral aspects of the temporal poles, usually more prominent on the left (Figs. 9.8 and 9.9). Although uncommon, preferential involvement of the right temporal lobe can occur and results in a more behavioral syndrome (the so-called right-temporal variant FTD [20]).

The pathological findings in svPPA are more frequently TDP-43 related, although there are case reports of abnormal tau deposition [21]. Genetics are rarely involved.

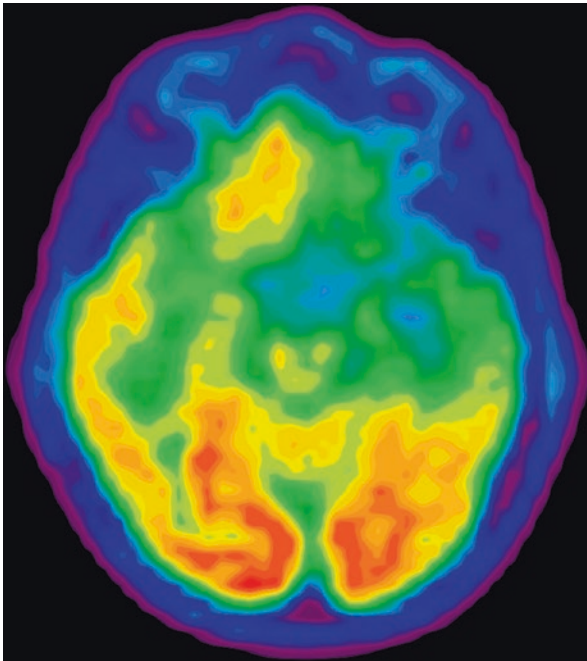


Fig. 9.8 FDG-PET (*axial view*). Note profound hypometabolism of the left anterior temporal lobe

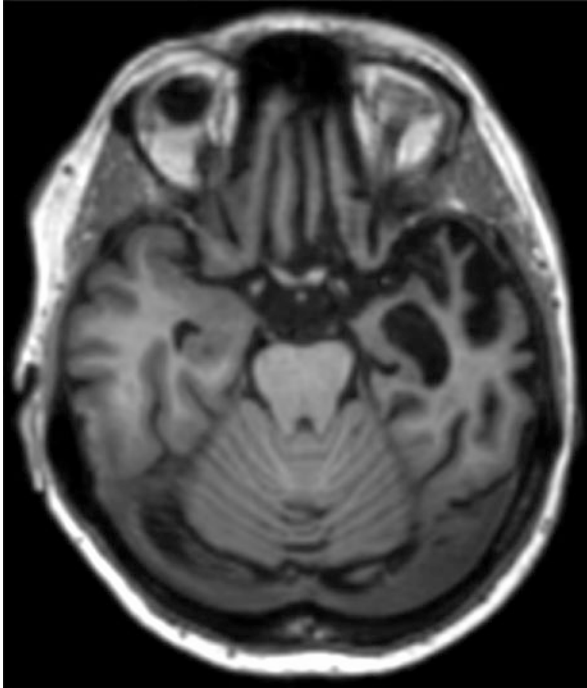


Fig. 9.9 T1-MRI (*axial view*). Note profound cortical atrophy of the left anterior temporal lobe with involvement of the hippocampus

Logopenic Variant PPA (lvPPA)

Logopenic variant PPA is the most recently described language variant [22]. The most salient features are *word retrieval* and *length-dependent sentence repetition* deficits (Table 9.1). Word retrieval or word finding deficits are most obvious during spontaneous speech or conversation. Speech is slowed, with frequent word finding pauses, but without agrammatism. Prosody is generally conserved, although the word-finding pauses disrupts the natural flow and can be frustrating to both the speaker and listener. Naming difficulties (anomia) may be present, but object knowledge is preserved so that the patient may describe objects in other more roundabout ways (circumlocution). Single word comprehension is also intact.

The disorder is thought to arise from damage to structures supporting phonologic short term memory (left temporoparietal areas). This type of memory is critical in word and sentence repetition. With disease progression, there is a gradual length-dependent sentence repetition deficit. The patient is able to repeat single words and

short sentences, but fails to repeat longer sentences, regardless of their grammatical complexity. A similarly length-dependent deficit will emerge affecting sentence comprehension.

Additional features include phonologic paraphasias (e.g., “greel” for “green”) during spontaneous speech and confrontational naming. Words are misspoken because of phonetic substitutions, but there is no distortion of the word sounds, as seen in *nfvPPA*.

PET and MRI imaging abnormalities involve the left temporoparietal junction (Figs. 9.10 and 9.11). When *lvPPA* is well characterized, the underlying pathology is most often Alzheimer’s disease, although there are published exceptions, with *FTD*-type pathology.

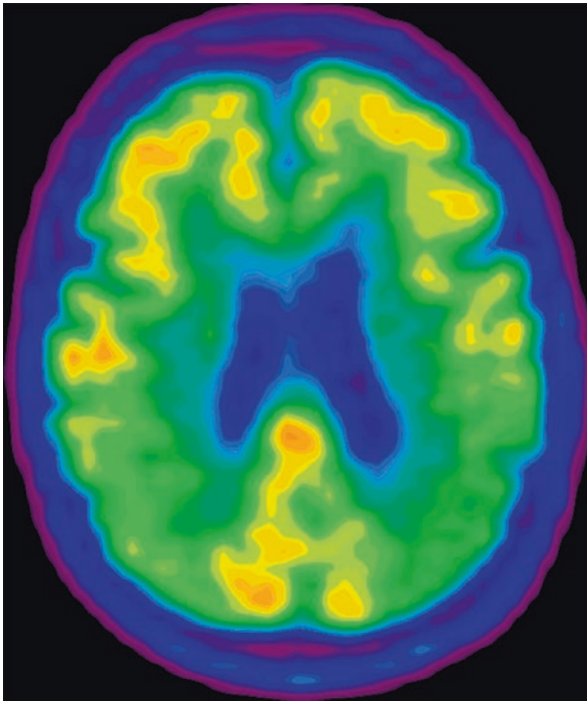


Fig. 9.10 FDG-PET (*axial view*). Note presence of bilateral parieto-temporal hypometabolism characteristic of AD, worse on the left

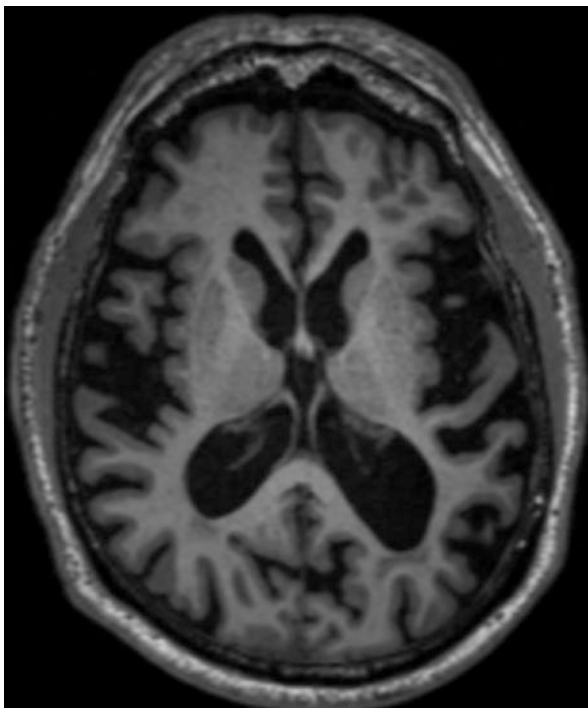


Fig. 9.11 T1-MRI (*axial view*). Note selective posterior perisylvian atrophy, much worse on the left

Differential Diagnosis

As for all conditions leading to gradual changes in mental status, reversible causes should be excluded. These involve endocrine, metabolic, and neoplastic or paraneoplastic conditions, central nervous system (CNS) infections, and dietary deficiencies.

The differential diagnosis for FTD will vary according to age. In younger patients it is often misdiagnosed as atypical depression, bipolar disorder, or late onset schizophrenia. Early-onset Alzheimer's disease can sometimes be difficult to differentiate clinically. Analysis of cerebrospinal fluid (CSF) for A-beta and tau proteins, demonstration of hippocampal atrophy on volumetric MRI, temporoparietal and posterior cingulate hypometabolism (rather than frontotemporal) on FDG PET, or the presence of amyloid on amyloid PET help accurately diagnose Alzheimer's disease. Late-onset major psychiatric disease should always raise suspicion for the presence of bvFTD.

In older patients, atypical depression, Alzheimer's disease, and Vascular Cognitive Impairment (VCI) are more frequent. Careful attention to the core criteria and a search for clinically consistent focal hypometabolism on PET and atrophy

MRI, as well as absence of significant or strategic vascular disease, will generally lead to an accurate diagnosis.

Because of its slow evolution, progressive aphasia is rarely confused with aphasias due to stroke or space occupying lesions. Alzheimer's disease represents the most common alternative diagnosis and is the most common pathological finding in lvPPA. CSF analysis for A-beta and tau, volumetric MRI and FDG or amyloid PET are helpful in this regard. CSF is typically normal in FTD; in Alzheimer's disease, the signature findings are elevated tau protein and reduced A-beta protein levels. If the clinical syndrome can be well characterized into one of the three PPA variants, the differential diagnosis becomes moot.

Treatment

As is the case for Alzheimer's disease, there are currently no approved or established treatments that address the underlying pathology or disease progression of FTD. Current approaches focus on addressing individual symptoms and promoting increased brain health and resilience (see healthybrains.org). Support and education of both patients and caregivers is critical. Education can be enhanced through referral to support groups and social work. The Association for Frontotemporal Degeneration (AFTD) and the Alzheimer's Association offer useful resources (www.theaftd.org & <http://www.alz.org/dementia/fronto-temporal-dementia-ftd-symptoms.asp>). Unfortunately, there still exist significant barriers to helping patients with FTD and their families access adequate care and resources [23].

Because judgment is often impaired early, usually resulting in poor job performance and impacting family finances, involvement of social work at the outset can help guide patients and caregivers through discussions of power of attorney. Additionally, patients with FTD and PPA may be eligible for "compassionate allowance" from the Social Security Administration and be fast-tracked for access to Social Security disability benefits (http://www.alz.org/living_with_alzheimers_social_security_disability.asp#compassionate).

Driving and gun safety should always be addressed as early as possible. Occupational therapists and state Division of Motor Vehicles may be used for more formal assessments of driving capacity.

Non-pharmacological management of behavioral and psychological symptoms in dementia (BPSD) should be part of a patient-centered, systematic, and evidence-based approach [24, 25]. An "ABC" (antecedent—behavior—consequence) approach [26] to understanding problem behaviors and adopting preemptive plans should be encouraged. The AFTD offers concrete examples of most problematic behaviors and specific interventions that have been helpful in preventing or mitigating their impact (<https://www.theaftd.org/wp-content/uploads/2011/09/Packet-Changes-in-behavior-chart.pdf>).

All current symptomatic pharmacologic treatments remain off-label. Serotonergic agents such as trazodone, sertraline, or escitalopram can be helpful in controlling

disinhibition, agitation, irritability, and obsessive/compulsive behavioral changes. Serotonergic agents are particularly helpful in PPA, especially when there is preserved deficit awareness that can lead to anxiety and depression.

Antipsychotics may be helpful if there is aggression or frank psychosis but have limited usefulness otherwise. Because of the higher risk of parkinsonism, atypical neuroleptics such as quetiapine, risperidone, olanzapine, aripiprazole, and possibly pimavanserin (recently approved for the treatment of psychosis in Parkinson's disease) are preferred.

Agents approved for the treatment of Alzheimer's disease have been de facto adopted in treating FTD [27], but data supporting such usage is lacking. In fact, cholinesterase inhibitors have been associated with increased agitation in bvFTD [28]. A possible role remains in the treatment of PPA, particularly for lvPPA or if Alzheimer's disease remains in the differential. Treatment with memantine has been found to be of no benefit to patients with FTD [29].

There may be a role for dextromethorphan/quinidine in the treatment of agitation. It is approved for the treatment of pseudobulbar affect and has recently been demonstrated to be helpful in the control of agitation in Alzheimer's disease [30].

ICD-10 Codes

- G30 Alzheimer disease
 - G30.0 Alzheimer disease with early onset
 - G30.1 Alzheimer disease with late onset
 - G30.8 Other Alzheimer disease
 - G30.9 Alzheimer disease, unspecified
- G31 Other degenerative disease of nervous system, not elsewhere classified
 - G31.0 Frontotemporal dementia
 - G31.01 Pick disease
 - G31.09 Other frontotemporal dementia

There are no specific billable codes for PPA. All three variants can be coded under G31.09, although lvPPA might better be coded under G30.0 or G30.1.

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Chapter 10

Parkinson's Disease

Shnehal Patel, Sergio Ramirez, Joseph Rudolph, and Hubert H. Fernandez

Clinical Pearls

- Parkinsonism is defined as bradykinesia plus the presence of either rigidity, tremor, or gait abnormality.
- PD is number 1 cause of parkinsonism, with asymmetric onset of symptoms that is slowly progressive and has an excellent levodopa response
- MSA can be considered when there is a presence of cerebellar signs along with parkinsonism without a significant levodopa response
- PSP can be considered with vertical gaze palsy, square wave jerks, and early onset of gait abnormality with falls.
- Drug-induced parkinsonism can occur in setting of any dopamine-depleting agent including typical antipsychotics, atypical antipsychotics, and anti-emetics.
- There are various options for treatment of PD that will depend on symptoms and age of patient; however, all patients should be encouraged to incorporate daily aerobic exercise.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer disease, affecting about 2% of the population over the age of 60. The prevalence of PD rises from 107/100,000 persons in age 50–59 years to 1087/100,000 persons in age 70–79 years [1]. Greater disease severity, and the

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presence of motor complications and cognitive issues have been correlated with higher costs and lower rates of employment [2–6]. Therefore, it is imperative to diagnose and optimally manage PD as early as possible.

Clinical Manifestation (History and Physical Examination)

Parkinsonism is defined by the presence of bradykinesia, in combination with either rest tremor, rigidity, or both. One of the main causes of parkinsonism is idiopathic PD.

Bradykinesia is best appreciated by investigating fine motor movements (e.g. finger tapping, hand grasps, wrist pronation and supination, toe tapping, and heel tapping), along with generalized body slowness (i.e. lack of spontaneous movement such as loss of facial expression [“masked facies”]), decreased weight shifting or leg crossing, slurred speech, and even hypophonia, due to improper movement of mouth and tongue. There may be bradyphrenia (slowness of thought), characteristically manifested by a delay in answering questions (even though the answer is correct). In the patient’s history, bradyphrenia manifests as slowness in performance of daily activities and decreased reaction times [7–9].

Tremor is evaluated with the hand resting supine on the lap, with the elbow gently resting against the body (i.e., not braced by the arm of the chair). This allows the classic “pill-rolling” tremor in the hands to emerge, although other body parts such as the chin, lips, tongue, legs and feet can also shake. Often, a distracting maneuver may help elicit the resting tremor—for example, having the patient close his or her eyes while performing a mental task such as subtractions or reciting the months of the year in reverse order. Actively suspending the hand in the air does not test resting tremor but rather assesses the presence of postural tremor, which is more commonly noticed in essential tremor (ET). However, if the postural tremor appears after a delay of a few seconds, it is considered a “re-emergent tremor” that suggest a parkinsonian tremor, rather than the true postural tremor seen in ET [10]. Classically, for idiopathic PD, the tremor is more likely to start in a unilateral limb and progress bilaterally, although up to 20% of PD cases do not manifest with any tremor.

Rigidity is assessed with the limb at rest and the examiner passively (and slowly) flexing, extending and rotating the joint. Rigidity can be further described as “lead pipe” rigidity when the increase in tone is smooth, or “cogwheel” rigidity, when tremor is superimposed on the stiffness. Activating the contralateral limb (such as asking the patient to open and close the right hand while one examines the left arm) may enhance the rigidity [11]. Some patients have an intrinsic difficulty in relaxing, which can be mistaken for parkinsonian rigidity. Finally, “gegenhalten” or paratonia may be detected if the resistance seems to be conscious or variable with direction of assessment, which can be determined by suddenly letting go of the limb and noting that the patient was holding it up all along [12].

Gait abnormality in PD includes the sudden stopping of walking that may occur upon the appearance of an obstacle or a doorway (freezing of gait), the inability to turn easily (leading to the en bloc turn as well as difficulty pivoting when attempting to sit back in a chair) and difficulty in initiating a step (gait ignition failure). Other gait features that can be noted include dragging the foot of the more affected side, decreased swing of the arm on the affected side and history of falls. Posture tends to be flexed or hunched, and more advanced patients may skew to one side. Interestingly, if lower extremity symptoms predominate or if freezing of gait seems prominent, this may suggest a Parkinson plus syndrome or a vascular parkinsonism [13, 14].

The Unified Parkinson's Disease Rating Scale (UPDRS, especially the Movement Disorder Society modified version) is the gold standard scale used to assess motor severity, track disease progression, and response to treatment. It can also be utilized in clinics for the Parkinson-specific motor examination [15].

Along with describing these motor symptoms, PD patients have significant non-motor features that are frequently associated with the disorder. These symptoms, at times, tend to be very disabling and require thorough investigation [16, 17]. These features are outlined below:

- Hyposmia, or the loss of the sense of smell, frequently predates the onset of motor symptoms by possibly 5–10 years [18, 19].
- Sleep disturbances may include one or more of the following [20]:
 - The most common sleep disturbance in patients with PD is insomnia, affecting up to 88% of patients [21, 22].
 - Restless leg syndrome [23, 24]
 - REM behavior disorder (“acting out one’s dreams” or purposeful actions during REM phase of sleep), which may predate the motor symptoms by years [25].
- Behavioral and cognitive symptoms including depression, anxiety, apathy, dementia, hallucinations, impulse control disorders all can be seen commonly in PD and require aggressive monitoring and treatment.
- Gastrointestinal symptoms include constipation, which occurs quite frequently, also often predating motor symptoms; gastroparesis; dysphagia (swallowing difficulties, which can predispose a patient to aspiration pneumonia); and sialorrhea (drooling)
- Urinary symptoms include urinary urgency and incontinence (resulting from bladder dyssynergia), along with nocturia
- Other autonomic symptoms include: erectile dysfunction, thermoregulatory dysfunction, and orthostatic hypotension (sense of lightheadedness when rising, can be seen as a result of PD as well as levodopa) [26, 27].
- Fatigue, which is often one of the most disabling non-motor symptoms of PD
- Seborrheic dermatitis

Diagnostic Approach

Upon evaluation in the clinic, if the above signs are present along with a history of having a sense of slowing down and other non-motor features, PD is high on the differential. Currently, there are no laboratory tests or imaging that can confirm the diagnosis of PD. Therefore, a thorough history and physical examination is key in diagnosing PD. The United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (UKPDBBC) have been used as gold standard diagnostic tool in PD research (Table 10.1).

Table 10.1 Approach to diagnosis of Parkinson's disease

Step 1. Diagnosis of a Parkinsonian syndrome
<ul style="list-style-type: none"> • Bradykinesia and at least one of the following <ul style="list-style-type: none"> – Muscular rigidity – 4–6 Hz rest tremor – Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction
Step 2. Exclusion criteria for Parkinson's disease (must answer 'no' to all these items)
<ul style="list-style-type: none"> • History of repeated strokes with stepwise progression of Parkinsonian features • History of repeated head injury • History of definite encephalitis • Oculogyric crises • Neuroleptic treatment at onset of symptoms • More than one affected relative (although several familial PD syndromes have now been described, so this is now often removed from the list of exclusionary criteria) • Sustained remission • Strictly unilateral features after 3 years • Supranuclear gaze palsy • Cerebellar signs • Early severe autonomic involvement • Early severe dementia with disturbances of memory, language, and praxis • Babinski sign • Presence of cerebral tumor or communication hydrocephalus on imaging study • Negative response to large doses of levodopa in absence of malabsorption • MPTP exposure
Step 3. Supportive prospective positive criteria for Parkinson's disease (three or more required for diagnosis of definite Parkinson's disease along with Step 1)
<ul style="list-style-type: none"> • Unilateral onset • Rest tremor present • Progressive disorder • Persistent asymmetry affecting side of onset most • Excellent response (70–100%) to levodopa • Severe levodopa-induced chorea • Levodopa response for 5 years or more • Clinical course of 10 years or more

Laboratory

There are no clinically available blood or cerebral spinal fluid tests for PD. Certain tests can be used to rule out mimickers, such as Wilson disease (which can manifest as a tremor, parkinsonian or dystonic syndrome) or thyroid abnormalities (hyperthyroidism can lead to tremors, hypothyroidism can present with slowness).

Imaging

Routine computerized tomography (CT) and magnetic resonance imaging (MRI) scanning are similarly unhelpful in diagnosing PD, except to rule out structural lesions. It is generally not necessary to obtain an imaging study if the clinical picture is clear.

Position emission tomography (PET) and single-photon emission computerized tomography (SPECT) scans can be useful in narrowing the diagnosis. A type of SPECT scan called a DaTscan™ (as the ligand binds to the dopamine transporter) distinguishes neuro-degenerative parkinsonian syndromes (which includes PD) from all other non-degenerative causes of parkinsonism (such as essential tremor, drug-induced parkinsonism and vascular parkinsonism) (Fig. 10.1) [28]. This scan, however, cannot distinguish PD from other “Parkinson-plus syndromes” such as multiple systems atrophy and progressive supranuclear palsy [17].

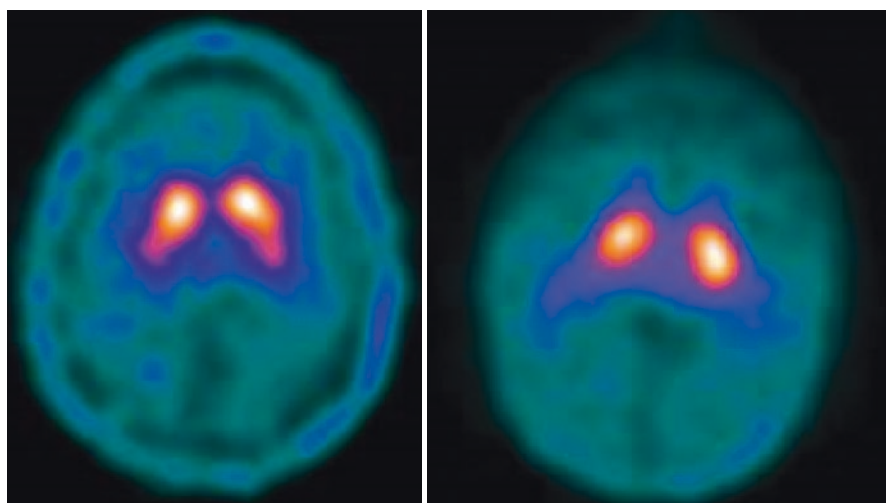


Fig. 10.1 DAT Scan with normal striatonigral activity (*left*) and abnormal activity characteristic of PD (*right*)

Ancillary Tests

Two ancillary diagnostic tests, olfactory loss and an abnormal metaiodobenzylguanidine (MIBG) scintigraphy (due to post-ganglionic sympathetic dysfunction in PD) have deemed reliable, with specificity >80% and may be used as a supportive criterion for diagnosis.

Diagnosis Criteria

Although the UKPDBBC criteria remains the research gold standard, the Movement Disorders Society has recently published the MDS Clinical Diagnostic Criteria for PD, incorporating both motor and nonmotor manifestations. The MDS-PD criteria incorporated many non-motor symptoms while retaining the central feature of parkinsonism (i.e. bradykinesia in combination with either rest tremor, rigidity or both). Similar to the UKPDBBC, after documentation of motor parkinsonism, the MDS-PD criteria proposed a list of absolute exclusions and red flags that argues against the diagnosis of PD, and supportive criteria that argue for PD diagnosis as the etiology of parkinsonism. Two levels of diagnostic certainty based on these positive and negative factors were proposed: clinically *established* PD and clinically *probable* PD [29] (Table 10.2).

Differential Diagnosis

For some of the non-motor features mentioned above, such as dementia, psychiatric features or orthostatic hypotension, if they are severe and out of proportion to the limb tremor and rigidity, a Parkinson-plus syndrome could be the diagnosis (such as multiple systems atrophy (MSA), progressive supranuclear palsy (PSP), cortico-basal degeneration (CBD), or Lewy body disease (DLB)). In general, Parkinson-plus syndromes should also be considered when the patient has extreme sensitivity or equivocal response to levodopa. One elusive differential diagnosis is vascular parkinsonism, which can manifest with a shuffling gait but may not typically have the tremor and limb rigidity of idiopathic PD. Vascular parkinsonism is typically the result of chronic small vessel disease affecting the periventricular area, basal ganglia, or parts of the brainstem, resulting in walking problems. Drug-induced parkinsonism should be considered when a patient presents with symmetric parkinsonism along with a significant history of neuroleptic or antiemetic use. In general, drug-induced parkinsonism is characterized by less tremors and postural instability and more rigidity, but this is not an absolute rule. It is important to consider essential

Table 10.2 Diagnostic criteria for Parkinson's disease

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS-UPDRS. See Fig. 10.2
Diagnosis of <i>Clinically Established PD</i> requires
<ul style="list-style-type: none"> • Absence of absolute exclusion criteria • At least two supportive criteria • No red flags
Diagnosis of <i>Clinically Probable PD</i> requires
<ul style="list-style-type: none"> • Absence of absolute exclusion criteria • Presence of red flags counterbalanced by supportive criteria <ul style="list-style-type: none"> – If one red flag is present, there must also be at least one supportive criterion – If two red flags, at least two supportive criteria are needed – No more than two red flags are allowed for this category
<i>Supportive criteria</i>
<ul style="list-style-type: none"> • Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as <ul style="list-style-type: none"> – Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver) – Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off • Presence of levodopa-induced dyskinesia • Rest tremor of a limb, documented on clinical examination (in past, or on current examination) • The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy
<i>Absolute exclusion criteria:</i> The presence of any of these features rules out PD
<ul style="list-style-type: none"> • Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (e.g., sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades) • Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades • Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria within the first 5 years of disease • Parkinsonian features restricted to the lower limbs for more than 3 years • Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism • Absence of observable response to high-dose levodopa despite at least moderate severity of disease • Unequivocal cortical sensory loss (i.e., graphesthesia, stereognosis with intact primary sensory modalities, clear limb ideomotor apraxia, or progressive aphasia)

(continued)

Table 10.2 (continued)

<ul style="list-style-type: none"> • Normal functional neuroimaging of the presynaptic dopaminergic system • Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is more likely than PD
<i>Red flags</i>
<ul style="list-style-type: none"> • Rapid progression of gait impairment requiring regular use of wheelchair within 5 years of onset
<ul style="list-style-type: none"> • A complete absence of progression of motor symptoms or signs over five or more years unless stability is related to treatment
<ul style="list-style-type: none"> • Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, nasogastric tube, or gastrostomy feeding) within first 5 years
<ul style="list-style-type: none"> • Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
<ul style="list-style-type: none"> • Severe autonomic failure in the first 5 years of disease. This can include <ul style="list-style-type: none"> – Orthostatic hypotension—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mmHg systolic or 15 mmHg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or – Severe urinary retention or urinary incontinence in the first 5 years of disease (excluding long-standing or small amount stress incontinence in women) that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
<ul style="list-style-type: none"> • Recurrent (>1/year) falls because of impaired balance within 3 years of onset
<ul style="list-style-type: none"> • Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 years
<ul style="list-style-type: none"> • Absence of any of the common nonmotor features of disease despite 5 years disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
<ul style="list-style-type: none"> • Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
<ul style="list-style-type: none"> • Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination

tremor (ET) when the patient has action tremors without rigidity and subsides with alcohol. Since ET also commonly afflicts the elderly, it is not uncommon for these patients to have some degree of bradykinesia. Enhanced physiologic tremors can be occur when the sympathetic nervous system is “over-stimulated” such as in hyperthyroidism, anxiety, and use of anti-asthma inhalers and steroids. Depression can be associated with slowness of movement (termed psychomotor retardation) but typically without tremors at rest or rigidity, and depressed mood is the main complaint.

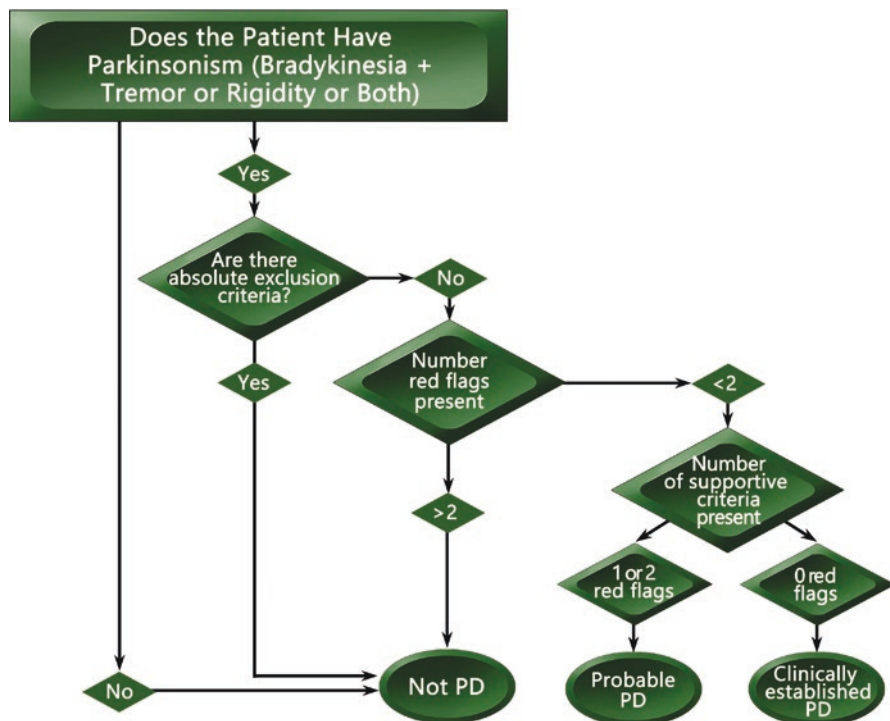


Fig. 10.2 Approach to diagnosis of Parkinson's disease

Therapeutics

Initiating treatment and choosing a drug are very individualized decisions. Age, disease severity, insurance and financial state, work status, and even the predominantly affected side can play a role in the timing of initiation and in pharmacological selection. The following discussion is to be used as a guideline that can be modified based on influencing circumstances. Figure 10.3 describes the suggested treatment approach. While general therapeutic principles should be practiced, it is critical to individualize therapy to the patient. Older patients are more predisposed to developing side effects from adjunctive PD medications, and less likely to develop levodopa-induced dyskinesias. Therefore, they are generally best initiated on levodopa, regardless of disease severity [30].

Table 10.3 summarizes an approach to selecting the initial therapy for a newly diagnosed patient with PD.

Levodopa is still the most efficacious anti-parkinsonian agent available [31]. There are multiple formulations of levodopa including immediate-release carbidopa/levodopa (Sinemet), carbidopa/levodopa controlled release (Sinemet CR), carbidopa/levodopa/entacapone (Stalevo), dissolvable carbidopa/levodopa (Parcopa)

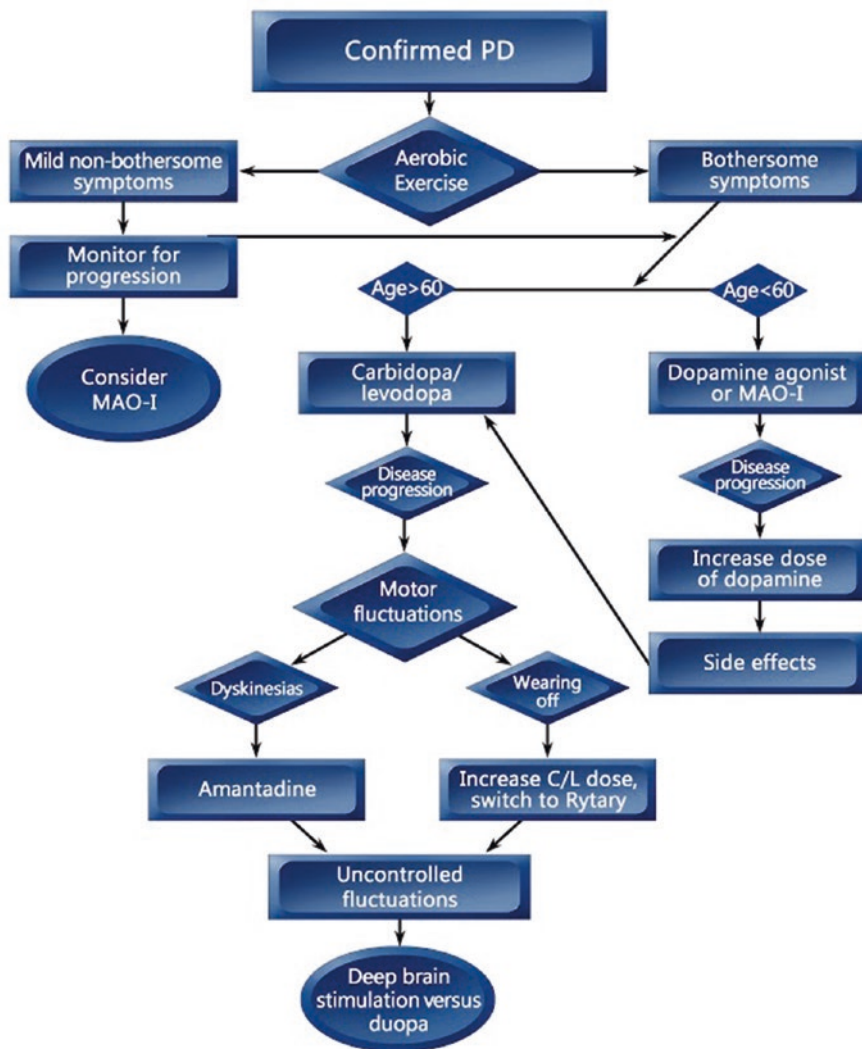


Fig. 10.3 Approach to management of Parkinson’s disease

and most recently, carbidopa/levodopa extended release (Ryтары). These medications are generally started three times a day (during awake hours to get most symptomatic benefit) and initially with meals (to minimize nausea and vomiting). Ryтары is the latest formulation of levodopa in capsule form (containing short-, medium- and long-acting levodopa) designed to extend benefit in patients who may be wearing off prior to their next dose.

The most recognized long-term risks of levodopa use are motor fluctuations and dyskinesias. They can occur in any PD patient, but these are more likely to be

Table 10.3 How to select an initial antiparkinsonian agent

Situation	Consider using this drug/class	Side effects/issues to consider or be aware of
Tremor predominant		
<ul style="list-style-type: none"> – Older patient – Younger patient 	<ul style="list-style-type: none"> – Dopamine agonist or levodopa – AC, amantadine, DA, LD 	DA side effects: sleep attacks in working patients and cognitive issues in the elderly
Young onset		
<ul style="list-style-type: none"> – Mild – Severe 	<ul style="list-style-type: none"> – Amantadine, MAOI, DA – Levodopa 	DA side effects: sleep attacks, compulsive behaviors and leg edema after long-term use
Older onset (regardless of severity)	Levodopa	
Associated with depression	Dopamine agonist	DA side effects
History of compulsive behavior	Levodopa	Be aware of worsening psychosis
Gait and postural predominance, falls, instability	Levodopa	

Medications listed by abbreviation: *AC* anticholinergics, *DA* dopamine agonists, *LD* levodopa, *MAOI* MAO-B inhibitors

experienced by younger-onset patients. While dyskinesias are more likely to occur with levodopa use than with dopamine agonists (discussed below), for many patients, particularly older ones, the side effect profile of levodopa is more favorable than that of an agonist. It is also useful to keep in mind that most dyskinetic activity, when they do occur, are generally non-bothersome or treatable.

Commonly used dopamine agonists include pramipexole and ropinirole (in a standard or extended-release formulation), rotigotine (in a patch) and apomorphine (injectable). Pramipexole, ropinirole and rotigotine can be used as initial monotherapy or as an adjunctive treatment to levodopa in the presence of wearing off or motor fluctuations. Apomorphine is used as a rescue agent when wearing-off is occurring, and when most other therapies have failed. As a class, dopamine agonists are less likely to cause dyskinesias and may be more effective for the control of tremors [32]. However, compared to levodopa, they have a higher likelihood of causing dopaminergic side effects such as light-headedness, sedation, confusion and hallucinations. In addition, idiosyncratic drug class adverse effects include leg swelling (which may not be responsive to diuretics), “sleep attacks”, as well as compulsive behaviors such as compulsive spending, pathological gambling, binge eating, punding, and hypersexuality.

Younger patients may similarly respond to amantadine, a drug of unclear mechanism of action, although purportedly acts as an NMDA-antagonist. This medication has a side effect profile includes hallucinations, insomnia, nausea, leg

swelling and 1% of the population may experience a purple lace-like appearing rash termed livido reticularis and so should be used with caution in older patients for PD symptom control. However, this medicine has multiple effects, including working to minimize levodopa-induced dyskinesias, and so for this latter purpose, it may be judiciously prescribed for patients of all ages [33].

Anticholinergic agents such as trihexyphenidyl and benztropine have been frequently used as levodopa-sparing options. Unfortunately, they have the side effects of confusion and hallucinations. In addition, perhaps they work only on tremor and less well on rigidity, though that may be debated.

The monoamine oxidase B inhibitors selegiline and rasagiline have been thought to possibly have a “neuroprotective benefit” although this belief continues to be debated to this day [34, 35]. They are generally well-tolerated, and are perceived to have a milder efficacy, and are therefore commonly used as initial monotherapy for PD. Rasagiline is also indicated as an add-on therapy to levodopa for motor fluctuations with relatively equal efficacy to COMT inhibitors [36, 37]. Because of the selective nature of its MAO inhibition, fears of drug-drug interaction and tyramine reactions, when using selegiline and rasagiline at recommended doses, are largely theoretical than a true practical concern.

Equally important, maintaining an active aerobic exercise regimen can be very beneficial in PD [38–40]. Options include stationary bike, treadmill, elliptical, yoga, tai chi, etc.

Figure 10.3 presents a suggested algorithm when treating a PD patient. When patients have symptoms that are bothersome enough to warrant treatment, age is an important factor to consider when deciding a medication. Older patients are at higher risk of side effects from dopamine agonists, and therefore carbidopa/levodopa is an appropriate first option. As the disease progresses, patients can experience motor fluctuations, as mentioned above. Older patients have a higher risk of cognitive impairment from PD medications. Therefore, in the presence of confusion, encephalopathy, delusions or bothersome hallucinations, it is imperative to simplify PD regimen by “peeling off” agents in this order:

1. Anticholinergic agents
2. Amantadine
3. MAO inhibitors
4. Dopamine agonists
5. COMT inhibitors
6. Levodopa

In PD patients with dementia, psychosis or sensitivity to medications, simply placing the on levodopa monotherapy may provide the greatest benefit-risk ratio.

Advanced treatment options including deep brain stimulation (DBS) and/or continuous levodopa infusion (Duopa) are considered when patients continue to experience motor fluctuations despite optimal use of conventional pharmacological treatment options. Duopa is a carbidopa/levodopa enteral suspension delivered through a PEG-J tube via an external pump, providing a stable level of levodopa, thereby alleviating motor fluctuations.

DBS was approved as a surgical treatment for PD by the Food and Drug Administration (FDA) in 2002 and currently is standard of care for advanced PD patients with significant motor complications, and for patients with treatment-refractory debilitating tremors. However, due to recent reports suggesting better quality of life among PD patients experiencing motor fluctuations for only 2 years, when receiving DBS as compared to best medical therapy, new guidelines have made DBS available for PD patients earlier in their disease course:

1. Diagnosis of PD for at least 4 years' duration with levodopa-responsive symptoms that are not adequately controlled with medication.
2. Motor complications from 4 months to 3 years
3. Motor complications of longer-standing duration.

Major advantages of DBS include its reversibility, and its ability to be modulated over time with disease progression or the occurrence of side effects or new symptoms. However, there is risk for infection, intracranial bleeding, and a patient should ideally be within close distance to a DBS center. DBS is contraindicated in patients with cognitive dysfunction. It is most ideal to have a multidisciplinary team when evaluating a patient for DBS with assessments from neurosurgery, neurology, neuropsychology and psychiatry (if needed). Patients and their families should have realistic expectations, including the recognition that DBS is not a cure and, generally speaking, with the exception of tremors and dyskinesias, the expectation that only PD symptoms that are responsive to their levodopa will respond to surgery.

ICD10 code

- Diseases of the nervous system G00-G99
 - Extrapyramidal and movement disorders G20-G26
 - Parkinson's disease G20-
 - Hemiparkinsonism
 - Paralysis agitans
 - Parkinsonism or Parkinson's disease NOS
 - Primary Parkinsonism or Parkinson's disease

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member of the Publication Committee for Dysport studies (Ipsen Pharmaceuticals) but he does not receive any personal compensation for these roles. Dr. Fernandez has received a stipend from International Parkinson and Movement Disorders Society for serving as Medical Editor of the MDS Web Site.

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Chapter 11

Atypical Parkinsonism

Brent Bluett

Clinical Pearls

- Slowing of vertical saccades or restricted downward gaze can differentiate PSP from other parkinsonian disorders
- Postural instability and falls are not commonly an early feature in Parkinson's disease but are prominent in PSP
- Midbrain atrophy on mid-sagittal MRI gives the characteristic "Hummingbird sign", which may help differentiate PSP from other forms of parkinsonism
- Unilateral "hand clumsiness" is the most common presenting motor symptom in CBD.
- Markedly asymmetric upper limb apraxia, rigidity, and dystonia help differentiate CBD from other forms of parkinsonism
- Early and pronounced autonomic dysfunction differentiate both forms of MSA from all other forms of parkinsonism and most adult onset cerebellar ataxias
- Lack of resting tremor, cerebellar ataxia, rapid progression, poor response to levodopa, and MRI abnormalities are useful in differentiating MSA from PD
- MSA patients need comprehensive care involving multiple medical disciplines (urology, cardiology, sleep medicine, gastroenterology)

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Atypical Parkinsonism

Introduction

Parkinsonism refers to a variety of syndromes unified clinically by the presence of bradykinesia—a disorder of motor function resulting in slow, small amplitude movements [1]. The most common form of parkinsonism is Parkinson’s disease (PD), while other forms are considered “atypical parkinsonism”, and are divided into sporadic, familial, and secondary etiologies [2]. The sporadic forms of atypical parkinsonism consist of Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), Multiple System Atrophy (MSA), and Dementia with Lewy Bodies [2, 3]. This chapter will focus on the diagnostic criteria and care paths for PSP, CBD, and MSA. DLB is discussed in a separate chapter. Figure 11.1 shows a summary approach to atypical parkinsonism.

Progressive Supranuclear Palsy (PSP)

Introduction

Progressive Supranuclear Palsy (PSP) is a sporadic atypical parkinsonian disorder which manifests as progressive bradykinesia and rigidity, ocular motility disturbances, and early falls [4]. Although rare in the general population, it is the most common atypical parkinsonian disorder—approximately 6% of all parkinsonian patients evaluated at a specialty clinic are diagnosed with PSP [2].

Since the initial recognition of the classic PSP syndrome (also called “Richardson syndrome” or “PSP-RS”), several clinical variants have been identified and are commonly referred to as “Atypical PSP” [5]. This sub-classification is based on the initial predominance of symptoms and includes speech/language disorders (PSP-SL) including progressive apraxia of speech (PSP-AOS) and nonfluent/agrammatic primary progressive aphasia (PSP-nfaPPA), cerebellar ataxia (PSP-C), corticobasal syndrome (PSP-CBS), frontal lobe cognitive of behavioral presentations (PSP-F) including behavioral variant frontotemporal dementia (bvFTD), ocular motor dysfunction (PSP-OM), parkinsonism resembling idiopathic Parkinson’s disease (PSP-P), postural instability (PSP-PI), primary lateral sclerosis (PSP-PLS), and progressive gait freezing (PSP-PGF). The unifying pathology of these disorders includes intracellular neurofibrillary tangle collection; the pathologic distribution and clinical severity differs with each subtype.

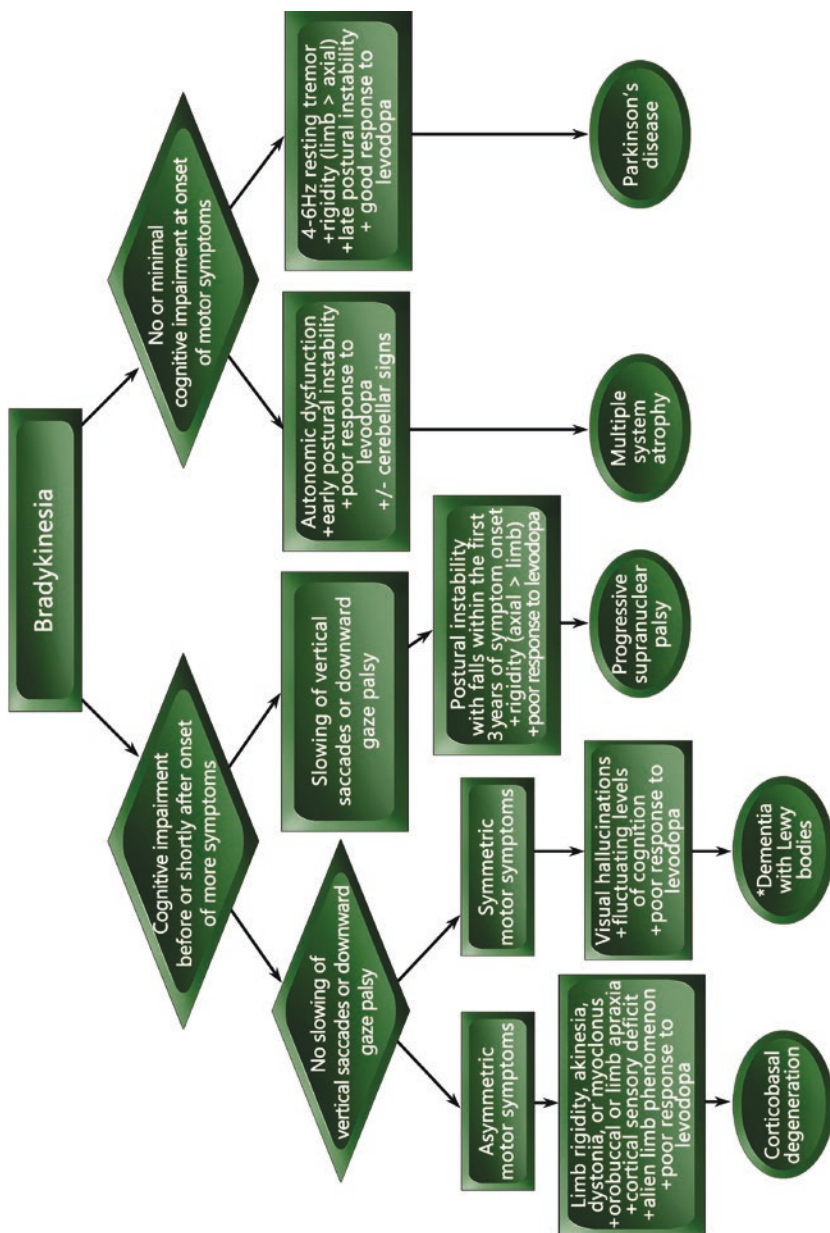


Fig. 11.1 Differential diagnosis of atypical parkinsonism

Clinical Manifestations

History

The average age of onset for PSP is 63 years old, a few years later than the average age of onset for Parkinson's disease [6]. The disease is rarely, if ever, seen in patients before age 40 and its diagnosis should be called into question in this age range [7]. The hallmarks of PSP are early postural instability with falls within the first year of disease onset, and vertical supranuclear gaze palsy [8].

Patients may initially experience personality changes, difficulty with balance, or vision disturbance. Bilateral bradykinesia is a common presenting symptom, seen in up to 88% of PSP patients presenting for the first time [8]. Most eventually pursue medical care after the onset of falls.

PSP patients experience their first fall a median of 16.8 months after onset of symptoms, falls after symptom onset take approximately 30 months in CBD, 40.8 months in vascular parkinsonism, 42 months in MSA, 54 months in DLB, and 108 months in PD [9]. Signs and symptoms shown to be associated with earliest falls (<2 years from symptom onset) include early cognitive dysfunction, symmetrical disease onset, axial rigidity, dysphagia, and eye movement abnormalities. Frontal lobe dysfunction manifesting as impulsivity and lack of insight further increases the risk of falls. Unexplained falls backwards, not associated with a loss of consciousness, are the most common clinical presentation of PSP.

Dystonia most commonly presents as blepharospasm, but may present as asymmetric limb or hemi-dystonia, or as axial dystonia [10]. Cervical dystonia is a common feature later in the disease, and can manifest as retrocollis, anterocollis, or torticollis [11]. Dystonia may be present as part of the natural course of the disease, or develop in response to levodopa administration. Dopaminergic medications may briefly improve the motor symptoms in the early stages of PSP, but more commonly there is little to no effect, and it may worsen gait abnormalities and balance [11].

Most patients eventually lose the ability to read or maintain persistent eye contact, and approximately 1/3 initially describe having blurred vision, eye discomfort, or double vision [10]. Patients rarely present with blatant complaints of being unable to look up or down. Eyelid dysfunction (ranging from a decreased blink rate to involuntary eyelid closure (blepharospasm), or failure to open upon command (eyelid freezing or apraxia of eyelid opening)) and difficulties with horizontal eye movements are markers of advanced stages of disease [12].

Early cognitive dysfunction is common in PSP, and may be the presenting symptom in up to 10% of patients [13]. Cognitive dysfunction seen in PSP usually manifests with impaired abstract thought, executive dysfunction, decreased verbal fluency, behavioral disturbances, and motor perseveration [14].

The disease progression in PSP is more severe and rapid than that seen in PD, with median survival ranging from 5 to 8 years [2]. With time, verbal fluency declines, axial rigidity and progressive immobility result, complete ophthalmoplegia may occur, and dysphagia worsens. Subsequently, death is most commonly secondary to respiratory complications, such as aspiration pneumonia or pulmonary emboli [15].

Physical Examination

The standard neurologic examination, with a focus on oculomotor evaluation, should be performed. Saccades, rapid eye movements to move the line of sight directly on the fovea, are evaluated by eliciting optokinetic nystagmus (OKN). This is commonly performed using a strip containing squares of alternating colors, asking the patient to look straight ahead while monitoring saccadic eye movements. Slowing of vertical ocular saccades (downbeat and upbeat) present early in the course of the disease, while horizontal saccades are affected later [16]. Vertical gaze paralysis occurs as the disease progresses, and may initially be overcome by the oculoccephalic maneuver [11]. Patients may present with the “procerus sign”: a wide-eyed look of astonishment or worry due to a combination of oculomotor abnormalities and rigidity, bradykinesia, and hypertonicity of the facial muscles [17].

The motor portion of the Unified Parkinson’s Disease Rating Scale (UPDRS-III) and/or the Progressive Supranuclear Palsy Rating Scale (PSPRS) are commonly administered. Patients with bradykinesia demonstrate delayed initiation of movement, progressive slowing, and/or decrement in amplitude with repetition [1]. Axial rigidity (clinically assessed by passive neck movement) is more pronounced than limb rigidity (tested by passive movement of the wrists, elbows, knees, and ankles). Patients are assessed for tremor at rest, with arms outstretched (postural tremor), and with movement (kinetic tremor). Tremor is a rare clinical feature of PSP-RS, but may be seen in PSP-P [1]. The classic gait seen in PSP is characterized by a stiff, broad-based posture, knee and trunk extension, and bilateral upper extremity abduction. Instead of the “en-bloc” turns seen in PD patients, PSP patients often pivot when they turn, which further increases the risk of falls [2]. Postural instability, an early and severe component of PSP, is assessed by the “pull test” (patients stand with feet apart and are pulled backwards at the shoulders by the examiner).

Cognition is typically assessed via the Montreal Cognitive Assessment (MOCA) or Mini Mental Status Examination (MMSE). Cognitive and behavioral changes are common in PSP, with deficits seen in numerous domains. Executive dysfunction is prominent, but memory and visuospatial deficits also occur. Apathy is frequently seen in PSP and patients may present concomitantly with impulsivity [18]. The severe episodic memory deficit observed in Alzheimer’s disease is not typically present in PSP, and recognition usually is largely preserved [13].

Diagnostic Approach for PSP

The clinical diagnosis of PSP is based primarily on history and physical examination, with supportive evidence provided by imaging. The definitive diagnosis is based on pathologic confirmation at autopsy. Figure 11.2 provides a diagnostic algorithm for parkinsonism.

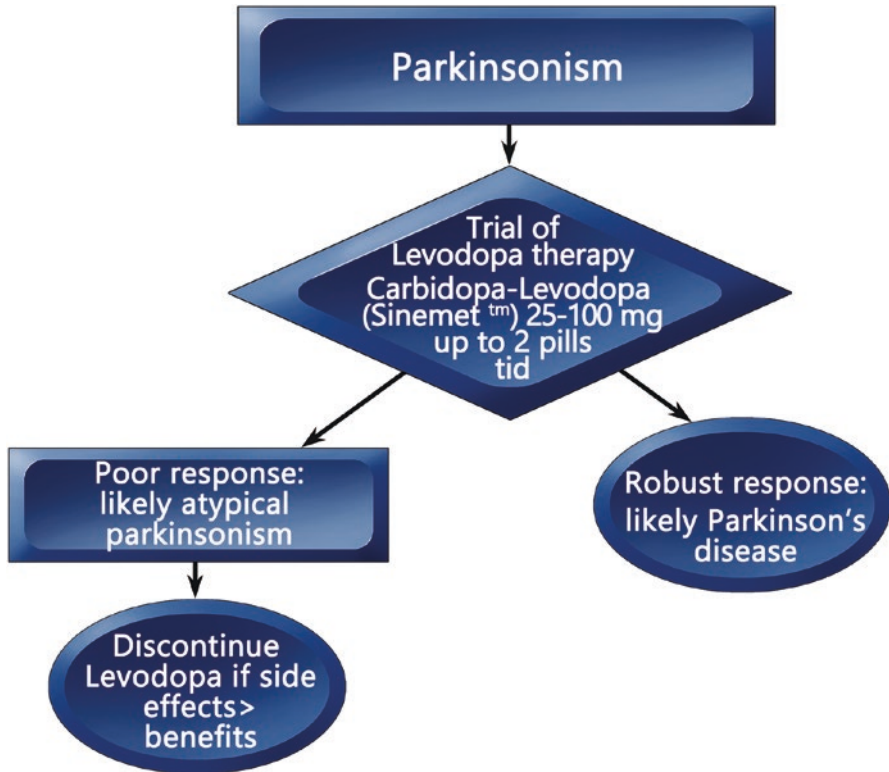


Fig. 11.2 Diagnostic algorithm for parkinsonism

Key history, examination, laboratory, and imaging criteria include:

History

- Prominent postural instability and falls within the first year of onset of symptoms
- Progressive onset of Parkinsonism (bilateral and symmetric bradykinesia, stiffness/rigidity, absence of tremor (unless PSP-P), worsening gait)
- May complain of blurred vision or difficulty reading (rarely complain of difficulty looking up or down)
- Early cognitive and behavioral abnormalities
- Rapid onset and progression of symptoms
- Limited or no response from levodopa

Neurologic Exam

- Slowing of vertical saccades or vertical supranuclear gaze palsy
- Prominent postural instability on pull test
- Bilateral and symmetric bradykinesia
- Axial > Limb rigidity
- Executive dysfunction, memory and visuospatial deficits on cognitive testing
- Table 11.1 shows the core clinical features of PSP

Imaging

MRI Brain

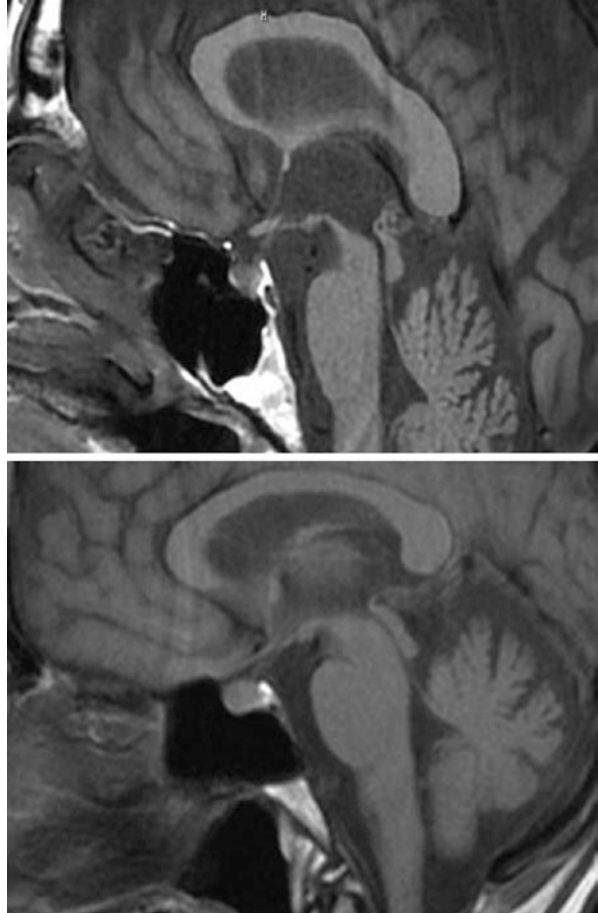
- (Fig. 11.3) Mid-sagittal MRI showing atrophy of the rostral midbrain tegmentum, caudal midbrain tegmentum, base of the pons, and cerebellum giving the appearance of the bill, head, body, and wing (respectively) of a hummingbird (“Hummingbird sign”) [19]
- A study using the A-P diameter of the midbrain and pons on mid-sagittal MRI, showed a midbrain measurement of <9.35 mm had 83% sensitivity and 100% specificity for PSP [20].
 - A midbrain to pontine ratio of <0.52 had 67% sensitivity and 100% specificity for PSP compared to MSA [20].
- Cortical atrophy with a frontal predominance is generally present as well

Table 11.1 Core clinical features of PSP

Levels of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
Level 1	01: Vertical supranuclear palsy	P1: Repeated unprovoked falls within 3 years	A1: Progressive gait freezing within 3 years	C1: Speech/language disorder, i.e., nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech
Level 2	02: Slow velocity of vertical saccades	P2: Tendency to fall on the pull-test within 3 years	A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	C2: Frontal cognitive/behavioral presentation
Level 3	03: Frequent macro square wave jerks or “eyelid opening apraxia”	P3: More than two steps backward on the pull-test within 3 years	A3: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	C3: Corticobasal syndrome

Levels with lower numbers are considered to contribute higher certainty to a diagnosis of PSP than levels with higher numbers. (From Hoglinger et al. 2017 [5])

Fig. 11.3 The “Hummingbird sign” in PSP (midbrain atrophy characteristic of PSP [top], a normal control is shown [below] for comparison)



DaT Scan

- FDA indicated for detecting loss of functional dopaminergic neuron terminals in the striatum [21]
- Reduced uptake is indicative of Parkinsonism, but does not differentiate PD, PSP, CBD, MSA, or DLB

Laboratory Testing

- Blood tests are typically of limited utility in diagnosing PSP
- CSF biomarkers are promising but need further validation

Genetic Testing

- Although considered a sporadic disorder, recent findings suggest there are likely predisposing genetic factors which are triggered in response to environmental factors such as oxidative stress [22].
- Currently, there are no genetic tests readily available to support or confirm a diagnosis of PSP.

Pathology

- Diagnosis of definite PSP can only be made by pathologic analysis upon autopsy
- Pathologically, PSP is characterized by aggregated tau protein forming neurofibrillary tangles in predominantly subcortical neurons, tufted astrocytes, and oligodendroglial inclusions [23]

Table 11.2 presents the diagnostic criteria for PSP.

Case Example

Example using the 2017 Movement Disorder Society Criteria for the Clinical Diagnosis of PSP:

A 64 year old gentleman presents to your office for evaluation of frequent falls. His first fall occurred two years ago - he was playing tennis and fell backwards after reaching up to hit the tennis ball. Since then he has had gradually increasing falls, many backwards, mainly due to imbalance and inability to react quickly. He is now afraid to walk, especially as occasionally his feet will ‘stick to the floor’ and he is unable to move. This happens most frequently when he starts to walk or goes through a narrow space. On examination, he exhibits bilateral symmetric bradykinesia, axial and limb rigidity, vertical supranuclear gaze palsy, and difficulty moving his feet when first starting to walk or going through a doorway.

Diagnosis: Probable PSP with progressive gait freezing.

Explanation: The patient has a gradually progressive worsening of gait with falls and freezing of gait within the first three years of symptom onset (A1). With evidence of vertical supranuclear gaze palsy (01), he meets criteria for probable PSP-PGF.

Differential Diagnosis

The differential diagnosis of atypical parkinsonism is summarized in Table 11.3 (see also Fig. 11.1).

Table 11.2 Research diagnostic criteria for PSP with degree of diagnostic certainty (Hoglinger et al. 2017) [5]

Diagnostic certainty	Definition	Supporting clinical/pathological observations	Predominant type	Terminology
Definite PSP	Gold standard defining the disease entity	Neuropathological diagnosis	Any clinical presentation	def. PSP
Probable PSP	Highly specific, but not very sensitive for PSP <i>Suitable for therapeutic and biological studies</i>	(01 or 02) + (P1 or P2)	PSP with Richardson's syndrome	prob. PSP-RS
Possible PSP	Substantially more sensitive, but less specific for PSP <i>Suitable for descriptive epidemiological studies and clinical care</i>	(01 or 02) + A1	PSP with progressive gait freezing	prob. PSP-PGF
		(01 or 02) + (A2 or A3)	PSP with predominant parkinsonism	prob. PSP-P
		(01 or 02) + C2	PSP with predominant frontal presentation	prob. PSP-F
		01	PSP with predominant ocular motor dysfunction	poss. PSP-OM
Suggestive of PSP	Suggestive of PSP, but not passing the threshold for possible or probable PSP <i>Suitable for early identification</i>	02 + P3	PSP with Richardson's syndrome	poss. PSP-RS
		A1	PSP with progressive gait freezing	poss. PSP-PGF
		(01 or 02) + C1	PSP with predominant speech/language disorder ^a	poss. PSP-SL
		(01 or 02) + C3	PSP with predominant CBS ^a	poss. PSP-CBS
The basic features B1+B2+B3 apply for all probable, possible, and suggestive criteria. Core clinical features are defined by their functional domain (ocular motor dysfunction [O], postural instability [P], akinesia [A], and cognitive dysfunction [C]), and stratified by presumed levels of certainty (1[highest], 2[mid], 3[lowest]) they contribute to the diagnosis of PSP ^a Probable 4R-tauopathy (i.e., either PSP or CBD)		02 or 03	PSP with predominant ocular motor dysfunction	s.o. PSP-OM
		P1 or P2	PSP with predominant postural instability	s.o. PSP-PI
		03 + (P2 or P3)	PSP with Richardson's syndrome	s.o. PSP-RS
		(A2 or A3) + (03, P1, P2, C1, C2, CC1, CC2, CC3, or CC4)	PSP with predominant parkinsonism	s.o. PSP-P
		C1	PSP with predominant speech/language disorder	s.o. PSP-SL
		C2 + (03 or P3)	PSP with predominant frontal presentation	s.o. PSP-F
		C3	PSP with predominant CBS	s.o. PSP-CBS

The basic features B1+B2+B3 apply for all probable, possible, and suggestive criteria. Core clinical features are defined by their functional domain (ocular motor dysfunction [O], postural instability [P], akinesia [A], and cognitive dysfunction [C]), and stratified by presumed levels of certainty (1[highest], 2[mid], 3[lowest]) they contribute to the diagnosis of PSP
^aProbable 4R-tauopathy (i.e., either PSP or CBD)

Table 11.3 Differential diagnosis of PSP, CBD, and MSA

Parkinson's disease
– Asymmetric onset of bradykinesia and 4–6 Hz rest tremor
– Marked and prolonged levodopa benefit
– Lack of early postural instability and falls
Dementia with Lewy bodies
– Hallucinations or delusions prior to the onset of parkinsonism
– Fluctuating levels of cognition with pronounced variations in attention and alertness
Alzheimer's disease
– Progressively worsening short-term memory loss with gradual onset of executive dysfunction, behavioral abnormalities, and cortical dementia
– Lack of prominent motor findings
Normal pressure hydrocephalus
– Subcortical dementia, urinary incontinence, wide-based magnetic gait
– Ventricular enlargement out of proportion to cortical atrophy
Vascular parkinsonism
– Multiple strokes, at least one involving the brainstem or basal ganglia
– Abrupt onset of symptoms without steady, progressive worsening
– Predominantly lower extremity parkinsonism
Frontotemporal dementia [50]
– Typical age of onset fourth to sixth decade
– Marked atrophy of frontal and temporal lobes on imaging
– 20–50% have first degree relative with FTD
Fragile X-associated Tremor/Ataxia Syndrome (FXTAS)
– Onset of ataxia, postural and kinetic tremor, parkinsonism, autonomic dysfunction, mild cognitive impairment with executive dysfunction, and peripheral neuropathy in males >50 years old
– May have family history of grandchild with Fragile-X syndrome or first degree relative with premature ovarian insufficiency (inability to get pregnant)
– MRI brain shows hyperintensity of middle cerebral peduncles (MCP sign) and white matter lesions
– Genetic testing shows premutation expansions (55–200 CGG repeats) in the fragile X mental retardation 1 (FMR1) gene
Spinocerebellar Ataxia ('SCA', types 1, 2, 3, 6, 7, 12, and 21)
– Lack of prominent autonomic dysfunction
– Young age of onset except SCA 6 (mean age of onset 55 y/o (range 31–77))
– Slowly progressive cerebellar ataxia
– Abnormal oculocephalic reflex
– Neuroimaging: Cerebellar and spinal cord atrophy, rarely with brainstem involvement
Creutzfeldt-Jakob disease
– Rapid progressive dementia (<1 year), myoclonus, akinetic mutism, extrapyramidal signs [8]

Treatment of PSP/Atypical Parkinsonism

Tables 11.4, 11.5, and 11.6 present the treatment of motor, non-motor, and neuropsychiatric symptoms of PSP/atypical parkinsonism.

Table 11.4 Treatment of motor symptoms of PSP

<i>Motor symptoms</i>
Parkinsonism (Bradykinesia, Rigidity, (rarely) Tremor)
<ul style="list-style-type: none"> • Trial of levodopa therapy <ul style="list-style-type: none"> – Carbidopa-Levodopa (Sinemet) 25–100 mg up to two pills tid Gradual titration is recommended to avoid side effects – 25–33% of patients will have a significant, sustained response to levodopa therapy – Dopamine agonists are generally avoided due to side effects and decreased efficacy
Postural instability/falls prevention
<ul style="list-style-type: none"> • Physical therapy <ul style="list-style-type: none"> – Training focused on increasing amplitude of movements (i.e. LSVT-BIG) [51] – Focus on postural stability/gait training – Balance, eye movement, and visual awareness training may improve gait in PSP [52] • Exercise <ul style="list-style-type: none"> – Core strengthening – Aerobic exercise (safe and as tolerated) • Occupational therapy <ul style="list-style-type: none"> – Home health assessment – Evaluation for lifting devices or wheeled mobility aides – Optimize upper limb function • Assisted walking devices <ul style="list-style-type: none"> – Cane, walker, wheelchair Weighted walker may help prevent falls backwards
Freezing of gait
<ul style="list-style-type: none"> • Rasagiline (≤ 1 mg/day) • Amantadine 100–200 mg bid (monitor for hallucinations or impaired cognition) • Cues (focus on line on ground to step over) <ul style="list-style-type: none"> – Weighted walker with laser light
Cervical or limb dystonia
<ul style="list-style-type: none"> • Botulinum toxin injections • Oral medications (Trihexiphenidyl, Baclofen, Clonazepam) are less effective and generally avoided due to side effects
Eyelid dysfunction (blepharospasm or apraxia of eyelid opening)
<ul style="list-style-type: none"> • Botulinum toxin injections • Oral medications are less effective • Eyelid crutches may provide benefit

Table 11.5 Treatment of non-motor symptoms of PSP/atypical parkinsonism

<i>Non-motor symptoms</i>
Constipation
<ul style="list-style-type: none"> • High fiber diet • Daily metamucil or prune juice • Miralax (17 g once or twice daily as needed) • Stool softeners (Colace)
Dream enactment behavior (RBD) and insomnia
<ul style="list-style-type: none"> • Melatonin • Clonazepam (monitor for excessive sedation, impaired cognition)
Daytime somnolence
<ul style="list-style-type: none"> • Treat comorbid insomnia and sleep apnea <ul style="list-style-type: none"> – Sleep study – Continuous Positive Airway Pressure (CPAP)/Bivalve Positive Airway Pressure (BiPAP) • Modafinil (Provigil™)
Sialorrhea
<ul style="list-style-type: none"> • Botulinum toxin injections • Glycopyrrolate (monitor for impaired cognition or balance)
Dysphagia
<ul style="list-style-type: none"> • Speech therapy <ul style="list-style-type: none"> – Bedside swallow evaluation – Modified barium swallow study • Monitoring swallow function • Eating and drinking strategies <ul style="list-style-type: none"> – Tuck chin while eating/drinking – Modified diet and fluids – Maintaining oral hygiene – Assistive mealtime devices • Discussion regarding placement of Percutaneous Endoscopic Gastrostomy (PEG) feeding tube

Table 11.6 Treatment of neuropsychiatric symptoms in PSP/atypical parkinsonism

<i>Neuropsychiatric symptoms</i>
Depression/anxiety
<ul style="list-style-type: none"> • Antidepressant <ul style="list-style-type: none"> – Recommend Selective Serotonin Reuptake Inhibitor (SSRI) or Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) – Avoid tricyclic antidepressants due to potential side effects
Pseudobulbar affect
<ul style="list-style-type: none"> • Dextromethorphan/Quinidine (Nuedexta™)

Corticobasal Degeneration

Introduction

Corticobasal degeneration (CBD) is a pathologic diagnosis which encompasses the clinical phenotypes of corticobasal syndrome (CBS), frontal behavioral-spatial syndrome (FBS), nonfluent-agrammatic variant of primary progressive aphasia (naPPA or NAV), and progressive supranuclear palsy syndrome (PSPS, a subtype of CBD with overlapping features of CBS and PSP) [24]. There is significant variation and overlap between these subtypes, with features of each seen as the disease progresses. CBD, along with PSP, is a four-repeat tauopathy classified as a sporadic form of atypical parkinsonism.

Clinical Manifestations

History

CBD rarely manifests before 50 years of age, and the mean age at onset is 60 years \pm 9.7 years [25]. Patients may develop cognitive, language, or behavioral changes before the onset of motor symptoms, leading to a misdiagnosis of Alzheimer's disease or frontotemporal dementia until approximately 3 years after symptom onset [2]. Initial motor symptoms of CBS include markedly asymmetric upper limb bradykinesia, rigidity, dystonia, and myoclonus [1]. Limb apraxia is pronounced in CBD—patients often describe an inability to perform gross or fine motor movements with the affected limb. Asymmetric “hand clumsiness” is the most common presenting symptom, seen in approximately 50% of patients. [2].

Based on a large series of pathologically confirmed cases of CBD, the most common abnormalities of higher cortical function include cognitive impairment, behavioral changes, limb apraxia, aphasia, depression, cortical sensory loss, and alien limb phenomenon. The most common motor findings include unilateral limb rigidity, bradykinesia/clumsy limb, postural instability, falls, abnormal gait, axial rigidity, tremor, limb dystonia, and myoclonus [24].

Speech difficulties are common in CBD, with dysarthria and progressive aphasia being the most common disturbances [24]. Nonfluent aphasia typically accompanies right sided motoric symptoms, while visuospatial deficits are associated with left sided motoric symptoms [1]. Left sided motoric symptoms are also more commonly associated with the ‘alien limb’ phenomenon (involuntary limb movements accompanied by a sensation that the limb had a will of its own), indicative of right parietal lobe involvement [26].

As with other forms of atypical parkinsonism, CBD progresses rapidly. Mean duration from symptom onset to death ranges from 5.5 to 7.9 years in various studies [27, 28]. Death is usually secondary to pulmonary complications or sepsis in the setting of prolonged immobility [27].

Physical Examination

Patients with bradykinesia demonstrate delayed initiation of movement, progressive slowing, and/or decrement in amplitude with repetition [1]. Unilateral limb rigidity (clinically assessed by passive movement of the wrists, elbows, knees, and ankles) is prominent in the affected upper limb, while lower limb and eventually axial rigidity tend to occur later in the course of the disease [24]. Tremor and focal myoclonus are both seen in CBD, the latter characterized by irregular, non-rhythmic jerking motions of extremities, most commonly induced by touch (‘stimulus-sensitive myoclonus’) [2, 24].

The combination of upper limb rigidity and dystonia at rest often presents as arm elevation, while the affected upper limb is often flexed and held against the body during ambulation. Aside from minimal to no arm swing in the affected limb, the gait in CBD resembles the ‘shuffling gait’ seen in PD, due to decreased stride length and diminished step amplitude [29]. Postural instability is assessed by the “pull test” (patients stand with feet apart and are pulled backwards at the shoulders by the examiner). Severe postural instability should alert the examiner for the possibility of the PSPS phenotype of CBD.

Oculomotor abnormalities in CBD are common and include saccadic rather than smooth pursuit [30]. Slowing of vertical saccades and vertical supranuclear gaze palsy are rare except in the PSPS phenotype of CBD.

Specific tests should be performed to evaluate for abnormalities of higher cortical function. Ideomotor apraxia (inability to perform goal-oriented movements) is tested by asking patients to imitate simple motions (such as giving a ‘thumbs up’). Ideational apraxia (inability to coordinate sequential motor movements) is tested by showing pictures of common objects, such as a comb, and asking the patient to pantomime their use [31]. Cortical sensory loss may manifest as agraphesthesia (inability to recognize numbers or letters written on one’s palm), astereognosis (inability to identify a common object when placed in the affected hand with eyes closed), or extinction (intact sensation of the affected limb unless touching the opposite limb at the same time) [32–34].

Cognitive assessment via MoCA or MMSE typically demonstrates deficits in attention and visuospatial domains, with executive dysfunction most pronounced in the FBS phenotype of CBD [24].

Diagnostic Approach for CBD

The clinical diagnosis of CBD is based primarily on history and physical examination, with supportive evidence provided by imaging. The definitive diagnosis is based on pathologic confirmation at autopsy. The essential features of CBD are summarized here (see also Fig. 11.1 and Tables 11.3, 11.7, 11.8).

History

- Lateralized difficulty using upper limb often described as “hand clumsiness”
- Gradual onset of asymmetric parkinsonism (bradykinesia, rigidity, less commonly tremor)
- Progressive language, cognitive, and behavioral decline
- Rapid onset and progression of symptoms
- Limited or no response from levodopa

Physical Exam

- Striking asymmetry, initially involving upper limb
- Apraxia (most commonly ideational, with ideomotor apraxia seen in later stages)
- Cortical sensory loss consisting of agraphesthesia, astereognosis, or extinction
- Minimal to absent arm movement of involved limb on gait assessment
- Upper limb rigidity and dystonia contributing to arm levitation at rest
- Focal myoclonus that is most commonly stimulus-sensitive
- Deficits in attention and visuospatial domains, as well as executive function

Imaging

MRI Brain or CT Head (Fig. 11.4)

Although imaging findings vary based on the CBD phenotype, there is typically asymmetric atrophy of the posterior frontal and parietal lobes, along with dilatation of the lateral ventricles in the affected hemisphere [35].

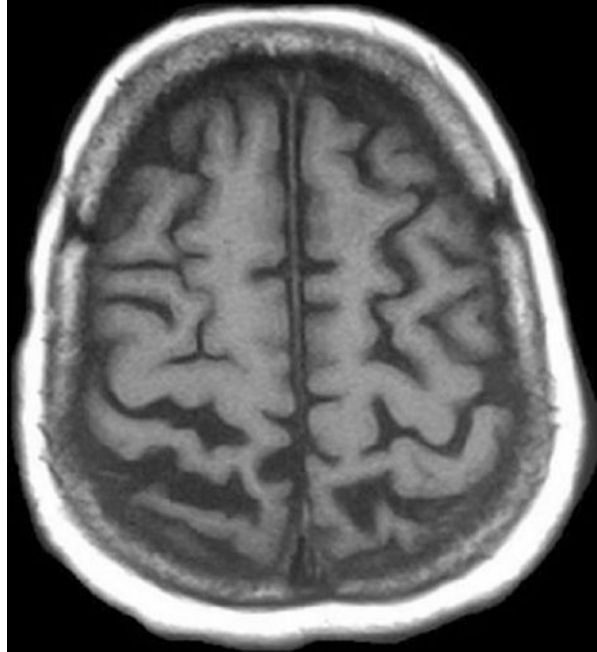
DaT Scan

- FDA indicated for detecting loss of functional dopaminergic neuron terminals in the striatum [21]
- Reduced uptake is indicative of Parkinsonism, but does not differentiate PD, PSP, CBD, MSA, or DLB

FDG-PET Scan

- Hypometabolism in the frontal, parietal lobes, and subcortical structures (thalamus, caudate nucleus, and putamen), with marked asymmetry between the two hemispheres [36]

Fig. 11.4 Asymmetric (*right*) parietal lobe atrophy indicative of CBD



Laboratory

- Blood tests are typically of limited utility in diagnosing CBD
- CSF biomarkers are promising but need further validation

Genetic Testing

- Genetic testing is unnecessary as virtually all cases of CBD are sporadic

Pathology

- Definitive diagnosis of CBD can only be made by pathologic analysis upon autopsy. Pathologically, CBD is characterized by tau-positive neuronal and glial lesions in the cortex and striatum, particularly astrocytic plaques and thread-like lesions in both white matter and gray matter. Neuronal loss is also seen in focal cortical regions and in the substantia nigra [37]

Diagnostic Criteria

Corticobasal degeneration remains a neuropathologic diagnosis performed at autopsy. Clinical diagnostic criteria to incorporate the most common phenotypes associated with CBD were recently developed (Table 11.7, 11.8) [24].

Differential Diagnosis

The differential diagnosis of PSP, CBD, and MSA is shown in Fig. 11.1 and Table 11.3.

Therapeutics (Treatment Care Path)

The therapeutic approach to atypical parkinsonism including CBD is shown in Tables 11.4, 11.5, and 11.6.

Table 11.7 Proposed clinical phenotypes (syndromes) associated with the pathology of corticobasal degeneration

Clinical phenotype	Features
Probable corticobasal syndrome	Asymmetric presentation of two of: (a) limb rigidity or akinesia, (b) limb dystonia, (c) limb myoclonus plus two of: (d) orobuccal or limb apraxia, (e) cortical sensory deficit, (f) alien limb phenomena (more than simple levitation)
Possible corticobasal syndrome	May be symmetric: one of: (a) limb rigidity or akinesia, (b) limb dystonia, (c) limb myoclonus plus one of: (d) orobuccal or limb apraxia, (e) cortical sensory deficit, (f) alien limb phenomena (more than simple levitation)
Frontal behavioral-spatial syndrome	Two of: (a) executive dysfunction, (b) behavioral or personality changes, (c) visuospatial deficits
Nonfluent/agrammatic variant of primary progressive aphasia	Effortful, agrammatic speech plus at least one of: (a) impaired grammar/sentence comprehension with relatively preserved single word comprehension, or (b) groping, distorted speech production (apraxia of speech)
Progressive supranuclear palsy syndrome	Three of: (a) axial or symmetric limb rigidity or akinesia, (b) postural instability or falls, (c) urinary incontinence, (d) behavioral changes, (e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades

Adapted from Armstrong, et al. 2013 [24]

Table 11.8 Diagnostic criteria for corticobasal degeneration

	Clinical research criteria for probable sporadic CBD	Clinical research criteria for possible sporadic CBD
Presentation	Insidious onset and gradual progression	Insidious onset and gradual progression
Minimum duration of symptoms	1 year	1 year
Age at onset	≥50 years old	≥50 years old
Family history (two or more relatives)	Exclusion	Permitted
Permitted phenotypes	<ol style="list-style-type: none"> 1. Probable CBD or 2. FBS or NAV plus at least one CBD feature: <ul style="list-style-type: none"> • Limb rigidity or akinesia • Limb dystonia • Limb myoclonus • Orobuccal or limb apraxia • Cortical sensory deficit • Alien limb phenomena 	<ol style="list-style-type: none"> 1. Possible CBD or 2. FBS or NAV or 3. PSPS plus at least one CBD feature: <ul style="list-style-type: none"> • Limb dystonia • Limb myoclonus • Orobuccal or limb apraxia • Cortical sensory deficit • Alien limb phenomena
Genetic mutation affecting tau (eg, MAPT)	Exclusion	Permitted
Exclusion options	<ul style="list-style-type: none"> • Evidence of Lewy body disease: classic 4 Hz Parkinson's disease resting tremor, excellent and sustained levodopa response, or hallucinations. • Evidence of multiple system atrophy: dysautonomia or prominent cerebellar signs. • Evidence of amyotrophic lateral sclerosis: presence of both upper and lower motor neuron signs. • Semantic- or logopenic-variant primary progressive aphasia. • Structural lesion suggestive of focal cause. • Granulin mutation or reduced plasma progranulin levels; TDP-43 mutations; FUS mutations. • Evidence of Alzheimer's disease, such as low cerebrospinal fluid beta-amyloid 42-to-tau ratio or positive ¹¹C-Pittsburgh compound B PET; or genetic mutation suggesting Alzheimer's disease (eg, presenilin, amyloid precursor protein). 	Same as probable CBS

Adapted from Armstrong, et al. 2013 [24]

CBD corticobasal degeneration, *CBS* corticobasal syndrome, *FBS* frontal behavioral-spatial syndrome, *MAPT* microtubule-associated protein tau, *NAV* nonfluent/agrammatic variant of primary progressive aphasia, *PSPS* progressive supranuclear palsy syndrome

Multiple System Atrophy

Introduction

Multiple System Atrophy (MSA) is a sporadic adult-onset neurodegenerative disorder consisting of autonomic failure and varying degrees of parkinsonism or cerebellar ataxia. Recently revised diagnostic criteria identifies two forms of MSA, both of which require autonomic dysfunction for diagnosis: MSA presenting with predominant parkinsonism (MSA-P; also known as “striatonigral degeneration”) or with predominant cerebellar ataxia (MSA-C; also known as “olivopontocerebellar atrophy”) [38]. Parkinsonism with early severe dysautonomia, cerebellar symptoms, gait disturbance, and lack of early cognitive impairment are most predictive of MSA [39].

Clinical Manifestations

History

The onset of MSA is generally in the sixth decade, and the disease rarely if ever presents before 30 years or after 75 years [2].

The initial symptom in males is typically erectile dysfunction, while most patients present to a physician with urinary disturbances (consisting of urgency, frequency, nocturia, incomplete bladder emptying, and incontinence) [40]. Other autonomic symptoms include orthostatic hypotension, “cold hands and feet” (Raynaud phenomenon), respiratory dysfunction (sleep apnea, inspiratory stridor), cardiac arrhythmia, and constipation.

Motor symptoms, consisting of parkinsonism (bradykinesia and rigidity, tremor, or postural instability) and/or cerebellar ataxia, typically develop after the onset of dysautonomia.

In contrast to Parkinson’s disease, motor symptoms tend to progress rapidly, and only approximately 30% of MSA patients have a clinically significant response to levodopa [1]. Bulbar dysfunction manifesting as dysphonia, dysarthria, and dysphagia is a prominent and rapidly progressing feature of MSA [41].

Although prominent cognition dysfunction is not an early feature of MSA, most patients eventually develop prefrontal dysfunction, which is more frequent and severe in MSA-P than MSA-C [42]. Pseudobulbar affect with emotional incontinence (inappropriate laughing or crying) is seen more commonly than in Parkinson’s disease.

The symptoms of MSA progress rapidly, and most patients become wheelchair bound within 5 years of symptom onset [41]. The median survival is 7–10 years (although wider ranges have been reported), and predominant cerebellar features and a younger age of onset (<60) predict a slightly better prognosis. Death is most commonly due to aspiration, sleep apnea, or cardiac arrhythmia [43].

Physical Examination

Standard clinical assessment of patients with suspected MSA should include general neurologic examination with focus on evaluation for pyramidal and Parkinsonian signs, cognitive testing and orthostatic vital signs.

Patients with bradykinesia demonstrate delayed initiation of movement, progressive slowing, and/or decrement in amplitude with repetitive movement of the hands, legs or feet [1]. Bradykinesia and rigidity are typically more symmetric in MSA than in PD. Resting tremor is infrequently seen in MSA (found in 13–29% of patients. [43, 44]. Patients are assessed for tremor at rest, with arms outstretched (postural tremor), and with movement (kinetic tremor). Postural and kinetic tremor, as well as stimulus-sensitive myoclonus (irregular twitching movements elicited by tapping on the patients fingers with their arms outstretched and palms facing up) are seen more commonly [1].

Cerebellar dysfunction manifests on examination most commonly as a wide-based, ataxic gait with severe postural instability (assessed by the “pull test”, patients stand with feet apart and are pulled backwards at the shoulders by the examiner). Limb ataxia is seen less frequently, but can be a prominent feature of MSA-C. Cerebellar oculomotor dysfunction can present as nystagmus, square wave jerks, jerky pursuit, and dysmetric saccades (in contrast to the slowing of vertical saccades and decreased range of extraocular movements in PSP) [38]. Patients most commonly present with a mixed cerebellar dysarthria with combinations of hypokinetic, ataxic, and spastic components of speech [45].

Dystonia is a frequent feature of MSA if anterocollis (forward flexion of the neck) is considered a form of cervical dystonia. Laryngeal dystonia manifesting as inspiratory stridor can occur, and levodopa therapy may result in facial and oromandibular dystonia [2]. Abnormal contractures of the hands and feet may be seen on examination, and patients may present with cold, violaceous extremities. The “Pisa syndrome” (severe lateral flexion of the spine causing the patient to lean sideways) or camptocormia (severe anterior flexion of the spine) may present as well [41].

Degeneration of the corticospinal tracts in MSA may manifest as pyramidal signs including spasticity, hyperreflexia, and the Babinski sign [46].

Cognition is typically assessed via MoCA or MMSE. Patients with MSA-P exhibit executive dysfunction with severe involvement of verbal fluency, visuospatial and constructional function. Cognitive impairment is milder in MSA-C, generally impacting only visuospatial and constructional function [42].

Orthostatic Vital Signs

Blood pressure and heart rate are assessed after the patient lies supine for at least 3 min, then again 3 min after standing. Diagnostic criteria for MSA defines orthostatic hypotension as a drop in blood pressure of at least 30 mm Hg or of diastolic blood pressure by at least 15 mm Hg with an undefined compensatory increase in heart rate [38].

Diagnostic Approach for MSA

The clinical diagnosis of MSA is primarily based on history and physical examination, with supportive evidence provided by imaging. The definitive diagnosis is based on pathologic confirmation at autopsy. The key features of MSA are shown here:

History

- Early severe autonomic dysfunction (erectile dysfunction, urinary disturbances, lightheadedness upon standing, respiratory difficulty, constipation, and/or cardiac arrhythmias)
- Rapid progression of parkinsonism (that is rarely responsive to levodopa) or cerebellar ataxia
- Postural instability and early falls (30 months after symptom onset on average) [9]
- Limited cognitive impairment relative to other forms of parkinsonism
- Lack of family history of similar symptoms

Neurologic Examination

- Orthostatic hypotension
- Typically bilateral and symmetric bradykinesia and rigidity
- Postural and kinetic irregular tremor (more common than resting tremor)
- Stimulus sensitive myoclonus
- Cerebellar features (wide-based ataxic gait, limb ataxia, oculomotor dysfunction, and dysarthria)
- Anterocollis, forward or sideward flexion of the spine, abnormal contractures of the hands or feet
- Cold hands and feet, with a dusky, purplish discoloration
- Pyramidal signs

Laboratory Testing

- Lab values are typically of limited utility in diagnosing MSA

Imaging

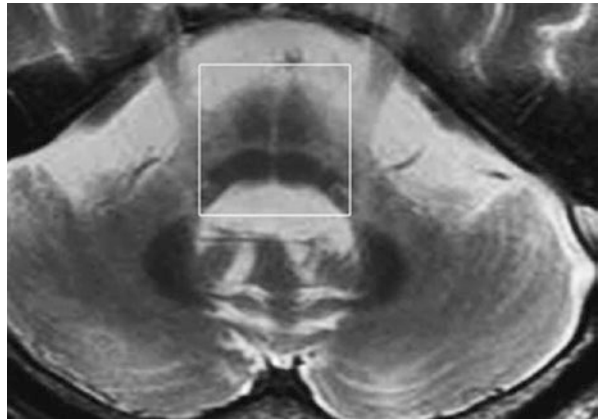
MRI Brain

- MSA-P and MSA-C:
 - Pontine and cerebellar atrophy involving the vermis and hemispheres (more common and severe in MSA-C) (Fig. 11.5) [47]

Fig. 11.5 Pontine and cerebellar atrophy in MSA-C



Fig. 11.6 “Hot Cross Bun” sign in MSA



- “Hot-cross bun” sign: cross-like degeneration of pontine fibers secondary to brainstem atrophy (Fig. 11.6)
- MSA-P (rarely MSA-C):
 - Putaminal atrophy and occasionally T2 hypointensity in the posterolateral putamen with slit-like hyperintensity of the surrounding rim [48]

DaT Scan

- FDA indicated for detecting loss of functional dopaminergic neuron terminals in the striatum [21]
- Reduced uptake is indicative of Parkinsonism, but does not differentiate PD, PSP, CBD, MSA, or DLB

FDG-PET Scan

- Hypometabolism in the putamen, brainstem, or cerebellum [38]

Genetic Testing

- Genetic testing is unnecessary as virtually all cases of MSA are sporadic

Ancillary Testing

- Cardiovascular and sudomotor autonomic testing may aid in differentiating MSA from PD and other adult onset cerebellar ataxias
- Urologic evaluation and urodynamic testing to identify the type of neurogenic bladder dysfunction
- Sleep study to evaluate for obstructive sleep apnea, nocturnal inspiratory stridor, and REM behavioral disorder (RBD)
- Cardiologic evaluation of arrhythmia and/or refractory orthostatic hypotension

Pathology

Diagnosis of definite MSA can only be made by pathologic analysis on autopsy. Pathologically, MSA is characterized by alpha-synuclein glial cytoplasmic inclusions leading to degeneration of striatonigral or olivopontocerebellar structures [49]. Definite MSA remains a neuropathologic diagnosis with features described above. Recently revised diagnostic criteria for the diagnosis of probable MSA (Table 11.9) and possible MSA (Table 11.10) are shown below.

Table 11.9 Criteria for the diagnosis of probable MSA

A sporadic, progressive, adult onset (>30 years/o) disease characterized by

Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic

Plus either of the following

Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability)

A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

Adapted from Gilman, et al. [38]

Table 11.10 Criteria for the diagnosis of possible MSA

A sporadic, progressive, adult onset (>30 years/o) disease characterized by

≥1 of the following features suggesting autonomic dysfunction:
 Otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA *and*

≥1 of the following additional features:

Possible MSA-P or MSA-C:

- Babinski sign with hyperreflexia
- Stridor

Possible MSA-P:

- Rapidly progressive parkinsonism
- Poor response to levodopa
- Postural instability within 3 y of motor onset
- Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
- Dysphagia within 5 y of motor onset
- Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
- Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum

Possible MSA-C:

- Parkinsonism (bradykinesia and rigidity)
- Atrophy on MRI of putamen, middle cerebellar peduncle, or pons
- Hypometabolism on FDG-PET in putamen
- Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

Plus either of the following

Parkinsonism (bradykinesia with rigidity, tremor, or postural instability)

A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

Adapted from Gilman, et al. [38]

Differential Diagnosis

The differential diagnosis of MSA is shown in Fig. 11.1 and Table 11.3.

Therapeutics (Treatment Care Path)

The treatment approach to MSA atypical parkinsonism is shown in Tables 11.4, 11.5, and 11.6. The treatment algorithm for symptomatic neurogenic orthostatic hypotension is shown in Fig. 11.7.

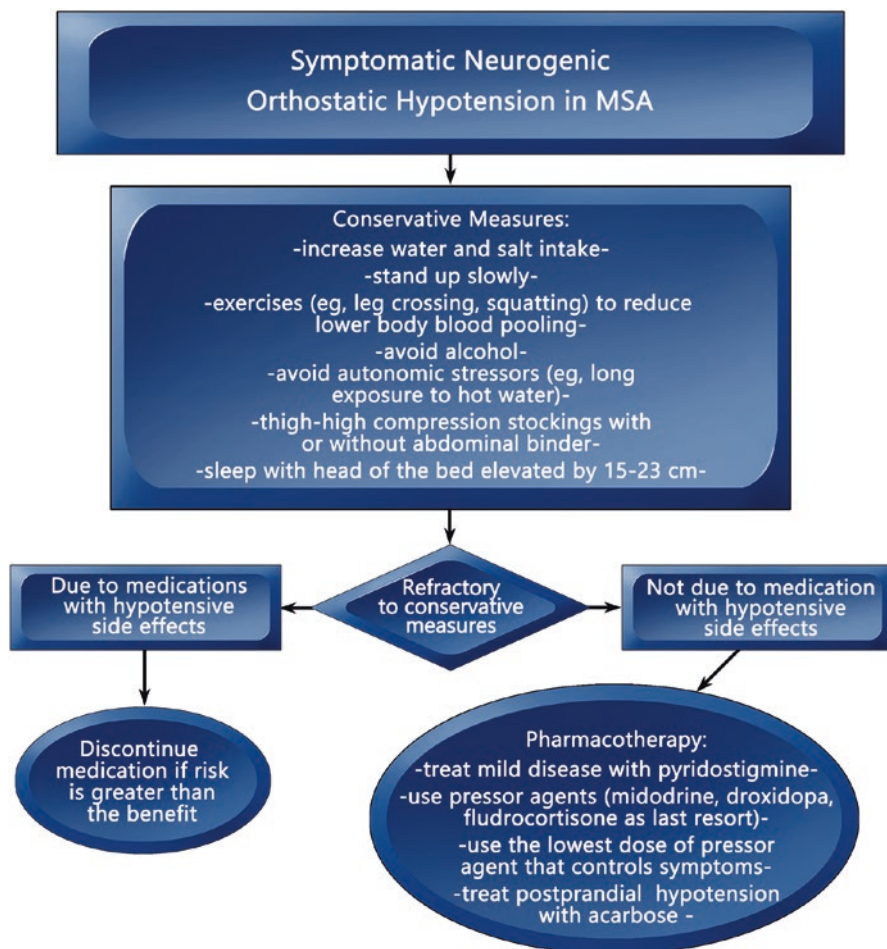


Fig. 11.7 Treatment algorithm for symptomatic neurogenic orthostatic hypotension

ICD 10 Codes

MSA Diagnosis: G90.3

PSP Diagnosis: G23.1

CBD Diagnosis: G31.85

Disclosures Dr. Bluett reports no disclosures.

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Chapter 12

Clinical Assessment and Management of Suspected Normal Pressure Hydrocephalus

Ronan Factora and Mark Luciano

Clinical Pearls

- Though the triad of NPH is distinct, alternative explanations for an individual's symptoms, particularly separate explanations for each of the three possible symptoms of cognitive impairment, urinary incontinence, and gait impairment, should be considered.
- Supplementary testing using validated tools (e.g. external lumbar drainage trial, high volume lumbar puncture) should be used to determine if individuals with suspected NPH will respond to surgical placement of a shunt.
- Smaller incision size and shorter surgical time are both related to better surgical outcomes and complication reduction.
- Placement of adjustable shunt allows for flow adjustments to be individualized where NPH symptoms worsen.
- Alternative causes for worsening symptoms should always be explored, including infections, shunt malfunction, and development of new undiagnosed conditions.

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Introduction

The triad of symptoms defining Normal Pressure Hydrocephalus (NPH) have been well documented and recognized—gait impairment, cognitive impairment, and urinary incontinence—with symptoms present in the context of enlarged ventricles. Prevalence of this disorder range from 0.6 to 6%, depending upon the study population, but it is believed that up to 70000–700,000 people in the United States are affected by this disorder [1]. Because of the overlapping prevalence of each of the symptom of the triad in the population of older persons, its evaluation poses a diagnostic challenge.

Clinical Manifestations and Diagnostic Criteria

NPH symptoms likely arise as result of the ventricular enlargement abutting the surrounding anatomical structures within the cerebrum and associated decreases in blood flow to that structure [2]. Gait impairment in NPH has been attributed to lateral ventricle compression of the fibers of the corticospinal tracts that supply the legs along the corona radiata [3, 4]. This is often observed as a reduction in gait speed (initially), development of balance problems, wide based gait, and problems with gait initiation. Urinary symptoms have been attributed to compression of sacral fibers along the corona radiate, which could the inhibit fibers supplying the bladder [3]. Urinary symptoms initially manifest an urgency and frequency, but frank incontinence develops typically because of gait problems interfering with an NPH patient's ability to get to act on the urge symptoms. Cognitive impairment typically manifests as slowness in processing speed as well as impairments in executive function and attention. Memory is typically preserved (Table 12.1).

Classically, the underlying mechanism for the development of ventriculomegaly has been thought to be due to impairment in the ability to absorb CSF, with resultant overload of fluid in a closed system leading to compression of brain structures. Current theories on the pathophysiology of NPH generally fall into one of two major schools of thought: the bulk flow theory where extraventricular obstruction of CSF flow, usually at the basal cisterns, is thought to be the underlying mechanism for NPH [5, 6], and the pulsation theory where decreased intracranial compliance leading to increased pulsatile stress on the ventricular walls is believed to be the cause of ventriculomegaly [7, 8].

Gait and balance problems are prevalent in older persons. Common causes of gait impairment in older persons are listed in Table 12.2. Cognitive impairment can range in severity from age-associated memory loss to impairment severe enough to affect function and support a diagnosis of clinical dementia. Prevalence of self-reported memory impairment has been as high as 22% in non-demented individuals [9]. Prevalence of dementia in individuals 65 and older ranges from 9 to 13% [10, 11], with prevalence increasing with age. Urinary incontinence is another common complaint in older individuals, with prevalence of this complaint ranging from 11 to 16% in men older than 65 and 36% in women older than 60 [12, 13].

Table 12.1 Comparison of cognitive deficits between NPH and other dementia types (X-present)

	NPH	Alzheimer's dementia	Vascular dementia
Memory impairment	Impaired retrieval	X	X
Executive dysfunction	X	X	X
Impaired visuospatial perception		X	X
Impaired language	Bradyphrenia	X	X
Impaired complex motor skills	Fine motor accuracy impaired	X	X
Psychomotor slowing	X		
Impaired attentiveness	X	Orientation impaired	
Impaired new learning		X	

Table 12.2 Commonly encountered causes of gait impairment in older persons

Alzheimer disease
Cerebrovascular disease: Binswanger disease, lobar stroke, lacunar stroke, vascular dementia
Lumbar canal stenosis
Osteoarthritis (hips, knees, feet)
Parkinsonism: Corticobasal ganglionic degeneration, diffuse Lewy body disease, Parkinson's disease, progressive supranuclear palsy
Peripheral neuropathy
Traumatic brain injury
Tumors

In NPH patients, gait or balance impairment is the most commonly encountered symptom, present in up to 89% of patients diagnosed with NPH [14]. As this is the core symptom of this disorder, absence of a gait or balance problem makes a diagnosis of NPH less likely, though atypical presentation of this disease has been reported. Absence of gait impairment in NPH typically portends poorer response to surgical intervention [15–17].

Cognitive impairment is present in up to 79% of cases, and urinary symptoms present in 44% [14]. Cognitive impairment is typically manifested by slowness in processing speed and executive function, with relative sparing of memory, which helps to distinguish NPH from other forms of dementia (Table 12.2). Urinary frequency often accompanies the above features, with frank functional urinary incontinence typically occurring as a result of NPH's associated gait impairment and inability of the individual to appropriately act on an urge to urinate.

Diagnostic Approach

Clinical presentation of an individual with gait or balance problems or findings of ventriculomegaly incidentally found on imaging of the brain should prompt consideration of the diagnosis of NPH. Clinical suspicion should be stronger if gait and/or

Table 12.3 Cleveland Clinic quadrant system for NPH categorization

	Typical NPH symptoms present	Atypical NPH symptoms or symptoms absent
Ventriculomegaly present	I	II
Ventriculomegaly absent	III	IV

I: Ventriculomegaly present and symptoms typical of NPH; consistent with Probable/Possible NPH

II: Ventriculomegaly present and symptoms atypical for NPH; consistent with Possible NPH; need to consider other explanations for symptoms, though accurate diagnosis of NPH still possible

III: No ventriculomegaly, but symptoms typical of NPH; need to identify alternative explanation(s) for symptoms, particularly gait symptoms (refer to Table 12.1)

IV: No ventriculomegaly, and symptoms atypical for NPH; alternative cause for symptoms very likely

balance problems are the initial or dominant clinical features. The additional presence of cognitive impairment or urinary frequency/urgency/incontinence helps increase the clinical probability that the entity being evaluated is in fact NPH.

A clinical paradigm using a quadrant system has been used clinically to help categorize patients and determine the probability that a patient has NPH or not [18] (Table 12.3). Individuals who fall within quadrants I and II have ventriculomegaly, with those in quadrant I having more typical features of NPH (gait impairment dominating, with additional symptoms of NPH) and those in quadrant II having more atypical features of NPH (cognitive problems or urinary symptoms dominate, with gait or balance problems less prominent). Patients falling into quadrant I can be categorized as having Probable NPH given nature of the person's symptoms (typical of NPH). Those in quadrant II may be categorized as having Possible NPH given the atypical nature of the individual's symptoms and the likelihood of other causes explaining the patient's symptoms. Individuals categorized in quadrants III and IV do not have ventriculomegaly, should not be evaluated for NPH, but should have other causes of their symptoms explored.

Imaging

Ventriculomegaly must be defined as the ratio of the lateral ventricles (at the level of the foramen of Monro) to the calvarium at the same level, with a value of >0.3 . CT or MRI of the brain without contrast should demonstrate the presence of ventriculomegaly, which is necessary for the diagnosis of NPH. Ventriculomegaly is typically reported as out of proportion to any atrophy that is present, though presence of atrophy does not exclude the diagnosis of NPH. Presence of cerebrovascular disease may identify an additional contributing factor to a person's symptoms. Figure 12.1 shows how ventriculomegaly looks.

Additional MRI evidence supporting the diagnosis of NPH includes presence of a flow void [19] as well as an increase in the callosal angle [20]. Presence of obstructive hydrocephalus due to an anatomical abnormality should prompt a

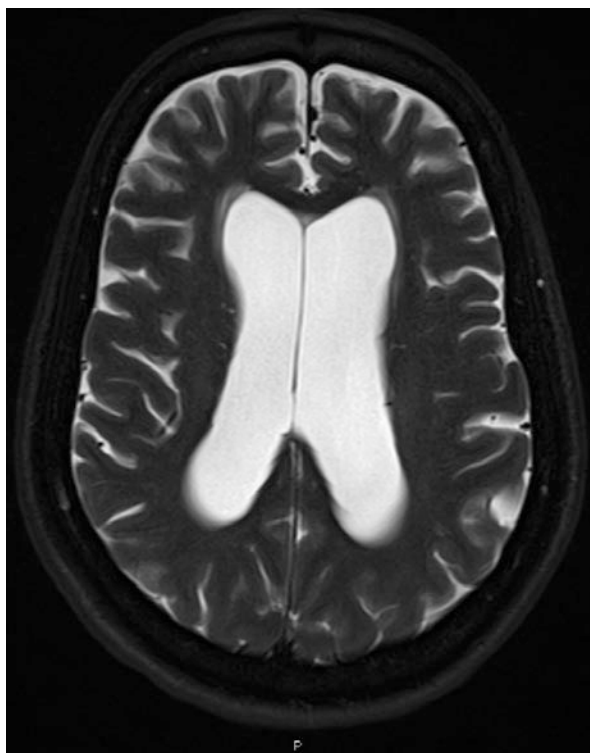


Fig. 12.1 Ventriculomegaly on CT of the brain; finding typical for individuals with a diagnosis of NPH

Table 12.4 Supplemental tests used to identify patients most likely to respond to shunting

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
High volume CSF tap test	26–62	33–100	73–100	23–42
External lumbar drainage	50–100	60–100	80–100	36–100
CSF outflow resistance	58–100	44–92	75–92	27–92
CSF outflow resistance (mixed population) ^a	46 ^b	87 ^b	56–92 ^c	34 ^b

^aIdiopathic and secondary NPH patients

^bRo threshold >18 mmHg/mL/min

^cRo thresholds vary from >8 mmHg/mL/min to >18 mmHg/mL/min

different evaluation and management plan, which would not include a drain trial. Surgical treatment of obstructive hydrocephalus typically involves an endoscopic 3rd ventriculostomy.

Several supplemental tests can be used to determine if a person with symptoms of NPH may benefit from shunt placement. Table 12.4 summarizes these

tests. Large volume lumbar puncture involves the removal of 40–50 cc of cerebrospinal fluid (CSF), with monitoring of NPH related symptoms for improvement after drainage. This procedure has reasonable sensitivity in identifying shunt responsive patients, but given the low specificity, it has been recommended that those with a negative response should not be excluded from surgical intervention [21–24]—the clinician/surgeon should make a clinical decision based on their overall findings.

An external lumbar drainage trial can be used to simulate placement of a ventriculoperitoneal shunt (VPS). The test involves placement of a lumbar intrathecal catheter followed by continuous drainage of CSF at a rate up to 10 cc/h for 72 h. Its sensitivity and specificity are better than that of a large volume lumbar puncture and could be used alone or after an inconclusive or negative large volume lumbar puncture [21, 23–25].

CSF outflow analysis (CSF Ro) measures impedance of flow in the CSF absorption pathways. Several techniques have been utilized to achieve this. One involves infusion of artificial CSF or saline solution at a known rate or at a constant pressure. Another method utilizes a single bolus of a known volume of fluid to measure brain conductance (which is 1/impedance). Given the differences in these techniques, the thresholds for abnormal ranges have varied. Sensitivity and specificity utilizing this type of analysis for purely NPH patients is quite good, though outcomes for trials including individuals with idiopathic and secondary NPH were not as favorable [21, 22, 26].

Other tests that have been previously utilized to identify individuals with suspected NPH who may benefit from VPS placement include cisternography and intracranial pressure monitoring. If elevated pressures are identified using intracranial pressure monitoring, this should lead to an investigation for secondary causes. Use of cisternography in the diagnostic evaluation of NPH has fallen out of favor given its poor accuracy [21].

Quantitative measurement of symptom improvements before and after a procedure can help ascertain if response to CSF removal is adequate to justify surgical intervention. The Raftopoulos method of measuring gait change is one method that could be utilized [27]. This scoring system utilizes a 10 m walk, which includes measures of total steps, time in seconds, and need for an assistive device while walking this distance. The Gait Score (GS) is measured as $1/(\text{steps (total number)} \times \text{time (s)} \times \text{assistance (1 if no assistance used; 2 if cane or walker used)})$. Measurements are taken before and after CSF removal to quantify performance differences. Pre- and Post- test measurements for GS are subsequently calculated utilizing these measures.

Change in Gait = $X^*/(X^* + X) \times 100$ (Where X^* = GS (post-trial or post-shunt) and X = GS prior to drain trial). If Change in Gait score is $>56\%$, it is considered to be an objective improvement in gait [27]. A 10 m walk velocity/gait velocity in combination with balance measures, Timed Up and Go, the 6 min walk test, or evaluation of balance or sway are other clinical options in measuring response to a trial and appropriateness for surgical intervention, though accuracy of these tests remain uncertain.

Neuropsychological Testing

Neuropsychological testing performed before and after a drain trial can also be used to quantify differences in performance. Many forms of cognitive testing have been used in published trials to detect change. Though broad based cognitive tests such as the Folstein Mini-Mental State Examination and the Montreal Cognitive Assessment could be utilized, they may be insensitive to the areas of cognitive function typically thought to be affected in NPH: executive function, processing speed, verbal memory [28, 29]. More focused forms of cognitive testing that may be able to detect changes in cognitive function may include Trails A and B, Symbol Digit (oral and written), and Hopkins Verbal Learning tests [30]. Despite these changes noted in neuropsychological testing before and after shunting, these indicators are not as good as a gait evaluation in predicting and NPH patient's response to shunt placement.

Changes in urinary symptoms typically are subjective. Urinary symptoms may include urgency, observations in urinary frequency, and also frank incontinence of urine. A diary documenting total number of voids per 24 h period before and after a drain trial may be able to quantify changes occurring around the trial period.

At the Cleveland Clinic Aging Brain Clinic, a scoring system utilizing all three symptoms has been utilized to determine the candidacy of a patient for shunt based on objective measurements and subjective symptom improvement.

Gait (G): 0 (Change in Gait ≤ 55); 1 (Change in Gait 56–69%); 2 (Change in gait $\geq 70\%$);

Cognition (C: based on z-scores for cognitive testing used): 0 (no significant changes in cognitive testing); 1 (1–2 areas of cognitive improvement); 2 (3 or more areas cognition improved).

Self-Improvement score (SI: based on subjective improvements in gait, cognitive function, and urinary symptoms observed by the patient): 0 (no significant improvement); 1 (mild-moderate improvement); 2 (significant improvement).

Total Score (TS) = G + C + SI.

If the Total Score was calculated as ≥ 3 , this individual was deemed to be an appropriate candidate for surgery.

Figure 12.2 illustrates the care path associated with the diagnosis of NPH.

Differential Diagnosis

Gait problems, cognitive impairment, and urinary incontinence alone are very frequent complaints in older persons. Alternative causes of each symptom must be considered in the process of evaluating persons with suspected NPH. In this context, it is more likely that causes of a person's symptoms are explained by multiple separate causes as opposed to a unifying diagnosis.

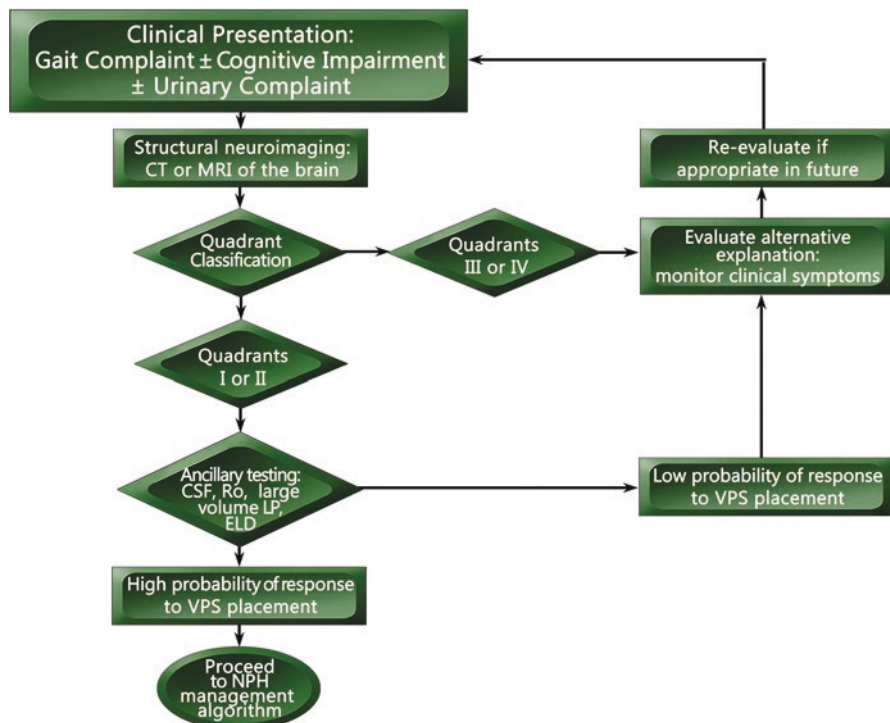


Fig. 12.2 Diagnosis of NPH

As gait impairment is the primary problem in NPH, alternative causes should be entertained. Parkinsonism (due to idiopathic parkinson's disease or diffuse lewy body disease) could be differentiated from NPH by its narrow base, responsiveness to visual clues, and accompaniment with resting tremor and/or bradykinesia. Lumbar canal stenosis typically is associated with low back pain, with intensity reduced when the individual is walking with a stooped gait. Gait impairment may be present in vascular dementia, depending upon the location of the vascular insult, but may be due to focal neurological deficits such as findings of lateralized hemiparesis, focal weakness in a limb, or cerebellar insults affecting coordination. Peripheral neuropathy predominantly affects sensation and could be identified with a positive Romberg test or abnormal findings on examination of light touch or proprioception. Gait impairment in Alzheimer's disease often is a late manifestation after years of progressive cognitive decline. Table 12.1 lists these common alternative causes of gait impairment.

Alternative causes for cognitive impairment include commonly encountered forms of dementia: Alzheimer's disease, Diffuse Lewy body disease, and vascular

dementia. In these disease processes, the cognitive impairment is often the dominating feature (though gait impairment is commonly present in Parkinson's disease Related Dementia as well as Diffuse Lewy body disease). Depression affects cognitive function and could affect gait, but the psychological symptoms in depression (anhedonia, psychomotor retardation, passive death wish/suicidality, poor sleep, poor appetite, low energy, guilty/ruminating thoughts) help to differentiate it from NPH. Differences in the types of impairment between these conditions is listed in Table 12.2.

Chronic urinary symptoms could be explained by commonly encountered conditions such as benign prostatic hypertrophy in men or overactive bladder/detrusor instability in women. Stress incontinence is often present in women, but usually explained by leaking related to increased intra-abdominal pressure (coughing, laughing, obesity). Though a good history and documentation of symptoms is effective in differentiating these conditions, urodynamic testing can be useful when additional information is needed.

Therapeutics

Ventriculoperitoneal shunt (VPS) is the mainstay of treatment for NPH. Placement of an adjustable shunt by an experienced surgeon allows for adjustment of drainage based on the patient's symptoms. Smaller incisions as well as shorter surgical length help reduce complications related to this surgery and improve outcomes. Complications include intracerebral hemorrhage related to catheter placement, subdural hematoma from overdrainage, and shunt infection.

Monitoring of symptom improvement (predominantly gait) is necessary to ensure continued benefit. Worsening of symptoms, headache, and any signs of infection should warrant an evaluation which may include evaluation of shunt function, removal of CSF to exclude infection, and shunt drainage rate adjustment.

Though the vast majority of devices continue to operate for years after placement, worsening NPH symptoms need to be investigated. If a follow-up evaluation reveals no clear cause, consideration should be made for an alternative explanation. In particular, shunt dysfunction should be ruled out as a source for recurrent symptoms. Not infrequently, older individuals who have NPH and have had VPS placement may still go on to be diagnosed with spinal stenosis, Parkinson's disease, or Alzheimer's disease. A re-assessment of these newly developing symptoms is worthwhile.

Figures 12.3 and 12.4 illustrate the care path associated with management of patients NPH in whom a shunt has been placed.

Fig. 12.3 Treatment of NPH

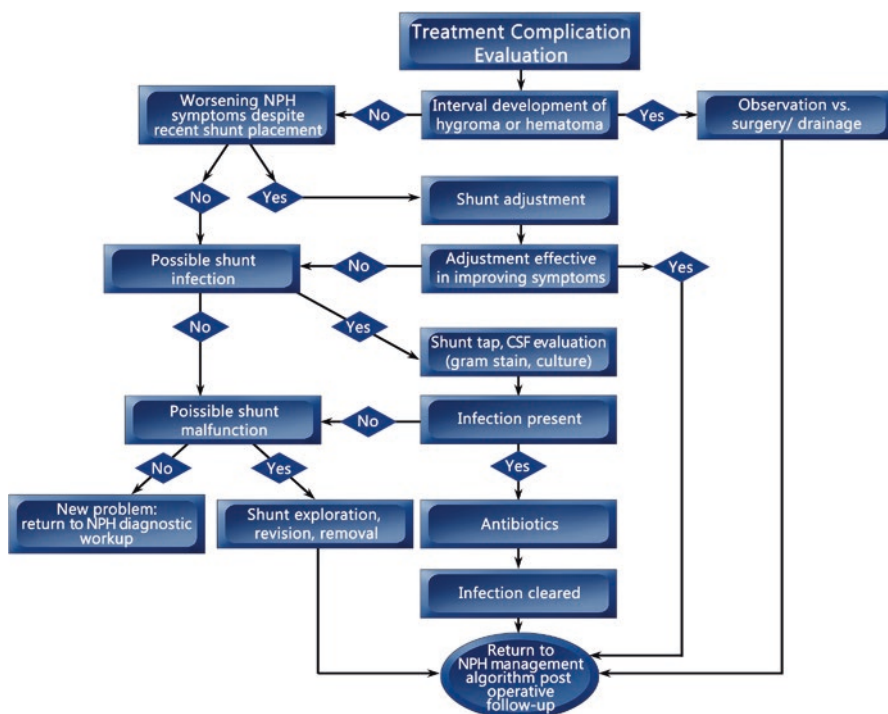
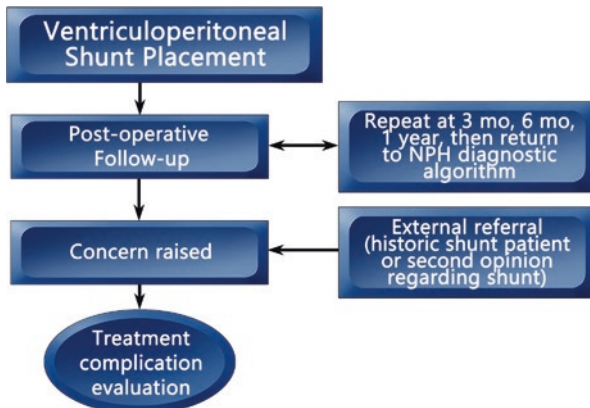


Fig. 12.4 Treatment of NPH (complication evaluation)

ICD-10 Codes

NPH: ICD-10 code G91.2

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Chapter 13

Chronic Traumatic Encephalopathy (CTE)

Sarah J. Banks

Clinical Pearls

- CTE at present remains a research diagnosis, confirmation is possible only at autopsy.
- Comorbidity is common at autopsy.
- Modifiable disorders such as major depressive disorders may present similarly to CTE but are treatable, the clinician should treat symptomatically.

Background

The concept of progressive neurodegenerative disease being associated with the head trauma sustained during contact sports has held various labels and descriptions: in 1928 the concept of “punch drunk” was introduced by Martland when he described the clinical presentation of 23 former boxers [1]. The symptoms he described included parkinsonian symptoms such as unsteadiness and staggering. In addition, he described cognitive changes; “periods of slight mental confusion” such that the “gallery gods often shout “cuckoo” at a fighter”. He stated that many cases remain mild, whereas others progress, again with more movement disorders including tremors, and only late in the disease and in the most severe cases did he report “marked mental deterioration”. The term “traumatic encephalopathy” was first used by Parker in 1934 to describe a neuropsychiatric syndrome also evident in retired

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boxers [2]. Another term used to describe the clinical presentation was dementia pugilistica, by Millspaugh in 1937 [3]. It was not until 1948 that Critchley used the terminology chronic traumatic encephalopathy [4]. Later on, Critchley changed his terminology to chronic progressive traumatic encephalopathy [5], to reflect the degenerative process that he observed in boxers.

While Martland posited a mechanistic and pathological theory of the punch drunk syndrome, he backed it up with autopsy series of patients who died from cerebral trauma but not those with the clinical syndrome that he described. The pathology underlying CTE was not described until Corsellis (1973) reported both gross and microscopic changes in brains of 15 boxers with dementia pugilistica [6]. Commonalities included septal and hypothalamic anomalies, cerebellar changes, degeneration of the substantia nigra and regional occurrence of Alzheimer's disease (AD) neurofibrillary tangles. Importantly, the tangles in these cases were mostly reported in the hippocampus and medial temporal gray matter, similarly to AD. These brains were reexamined by Roberts using immunocytochemical methods and found amyloid plaques in many of the brains, again similar to AD [7]. Others have reported subtle differences with tau being more commonly found in the depths of sulci in boxers [8], or distinct distribution from AD in a single boxer [9].

Until this century, descriptions of CTE-like syndromes were limited to boxers. This changed when Omalu described pathological changes in the brain of an American football players [10]. Since then, the diagnosis has become associated with American football, though further description in boxers, as well as hockey, rugby and other sports with a contact component, as well as soldiers, have been described. The recent descriptions in football players often have more neuropsychiatric or cognitive symptoms and fewer movement symptoms than described in early boxing cases.

CTE has been described most extensively by the Boston University group, who have described the most extensive collection of pathological [11–13] and clinical findings [14, 15]. They, and many others, describe CTE as a tauopathy with a unique neuroanatomic distribution, occurring as a result of rTBI. They have proposed research diagnostic criteria, discussed below.

Tau Protein

Tau is a microtubule-associated phosphoprotein whose role in the brain is to stabilize intracellular microtubules, which are important in intracellular transport of organelles, neurotransmitters etc. Tau has six isoforms, which in turn can be combined into two functionally distinct categories: with either three repeats or four repeats of the microtubule-binding domain. The isoforms or combinations thereof are associated with different pathologies (for review see Villemagne [16, 17]). It is usually soluble, but in pathological states becomes insoluble through hyperphosphorylation leading to aggregation into neurofibrillary tangles (NFT), and lack of normal microtubule stabilizing function. These interfere with axonal transportation leading to cell death, and are found most commonly in AD, frontotemporal lobar

degeneration due to tauopathy, corticobasal degeneration, progressive supranuclear palsy and more recently CTE [18]. However, NFTs are also common incidental findings in patients who have died without reported clinical changes, and in cases where clinical symptoms were evident, the distribution of NFTs in the brain is frequently independent of regions related to those symptoms [19]. The isoform of tau seen in the brains of those diagnosed with CTE has been described as similar to that found in AD [20]. Importantly, some have suggested that tau spreads between cells in a similar mode to prions, perhaps explaining their role in multiple neurodegenerative diseases [21], and generally the topography of the tau depositions within the brain is distinctive for each disorder (e.g., early deposition in the medial temporal lobe in AD) with preferential distribution in the depths of cortical sulci and around blood vessels in CTE.

Relationship of Head Injury to CTE

Assuming CTE is caused by tau in the brain which has accumulated in response to head injury, how do we quantify the required head injury and how can we know that a head injury or repeated injuries are sufficient to cause the pathology? Several different terms are used to describe head injury in relation to CTE. Concussion is frequently one of those terms, and has been defined in various ways, but most frequently in a recent literature using the Zurich criteria [22]. The criteria define concussion as “a complex pathophysiological process affecting the brain, induced by biomechanical forces” and lists potential symptoms including “rapid onset of short-lived impairment of neurological function that resolves spontaneously. However, in some cases, symptoms and signs may evolve over a number of minutes to hours”. This definition remains vague and subjective [23] adding further uncertainty to the trauma background necessary for CTE. Some have argued that a single head injury can trigger the pathological cascade of CTE [24] but this also remains controversial.

While some have cited concussion as a likely mechanism for CTE, others have suggested that multiple subconcussive blows could be important [25]. Knowledge of the necessary or sufficient head injury to cause CTE is elusive, although better understanding may be important in protecting athletes and others.

Proposed Pathology Criteria for CTE

Early descriptions of gross pathological changes include damage to the “copora striata, corona radiata and basal ganglions” as well as “traumatic punctate cerebral hemorrhages, hydrostatic disequilibrium of spinal fluid, cerebral edema etc.” according to Millspaugh ([3] p. 301). Other changes that are commonly reported include cavum septum pellucidum, loss of neurons in the substantia nigra, locus coeruleus and dorsal raphe. More recently, CTE has been defined pathologically as

deposition of hyperphosphorylated tau in neurofibrillary tangles, threads and astrocytes, as well as variable axonal and transactive response DNA-binding protein 43 (TDP-43) pathology [11]. The tau is distributed in a distinct pattern from other tauopathies, with particular concentration in the depths of the cerebral sulci, often surrounding penetrating cortical blood vessels. The distribution is also often focal, as opposed to distributed, and may involve the neocortex, medial temporal lobe, basal ganglia, diencephalon and brain stem. McKee [13] proposed a staging scheme, with disease limited to the cortex for stages I and II but subcortical pathology evident in stages III and IV. Some have diagnosed CTE in addition to other pathologies including ALS [12, 13]. Bieniek and colleagues (2015) compared neurodegenerative disease brain bank samples in Florida for men with a history of contact sport exposure and matched controls. Most men who were in the contact sports group ($n = 54$) had played football ($n = 34$) but there were others who were boxers, baseball players, basketball etc. Thirty-five of the men had been in the armed forces [26]. Of 198 control cases, 33 had some history of head trauma. Of the 21 contact sports players who were considered to have CTE tau pathology, in 17 cases it was limited to the frontal and parietal lobes. No CTE pathology was found in the controls, including those with documented head trauma. Given that these samples were from a neurodegenerative disease brain bank, they already had non-CTE diagnosis. These were varied and included AD, AD with Lewy body disease, pure Lewy body disease, ALS and FTLN. This is similar to the Boston University autopsy results, where the majority of cases described by McKee (2013) also met pathological criteria for another progressive neurodegenerative disorder. Indeed, in a systematic review, Gardner et al. (2014) pointed out that in metaanalysis of 85 autopsies on athletes only 20% had “pure” CTE, the remaining either had CTE plus another neuropathology and 24% had no neuropathology.

The diversity of comorbidities is important given the notion that tau can accumulate in association with normal aging, opiate abuse [27], temporal lobe epilepsy [28] as well as various pathologies, and the lack of regional relationship with symptoms specific to CTE (or, for that matter, the lack of symptoms specific to CTE). This lack of specificity both on a pathological and clinical level has led some to question whether CTE is, in fact, a stand alone diagnosis or if it reflects a reduction in cerebral reserve in response to head injuries. Such loss of cerebral reserve would lead to a heightened vulnerability to diseases of late life, and would account for the variability seen in symptoms and the tendency for combined presence with other disorders [29–31].

There are three sets of proposed pathological criteria for CTE, by McKee [13], Omalu [32], and Victoroff [33]. These overlap in some ways but differ in terms of presence of atrophy, location and extent of medial temporal tau, presence of amyloid deposits etc. In response to the need for better pathological definition of CTE, there was a recent National Institute of Neurological Disorders and Stroke (NINDS)/National Institute of Biomedical Imaging and Bioengineering (NIBIB) consensus conference, held in 2013, where several neuropathologists evaluated 25 cases of tauopathy including ten CTE brains (notably, seven of these also had AD like amyloid plaques, and other comorbidities were also described). Agreement was good but only one pathognomonic finding was agreed upon: CTE features “an accumulation of

Table 13.1 Supportive features of CTE pathology agreed upon by NINDS/NBIB consensus (2013)

<i>Supportive neuropathological features of CTE (p-Tau)-related pathologies.</i>	
1.	Abnormal p-tau immunoreactive pretangles and NFTs preferentially affecting superficial layers (layers II–III), in contrast to layers III and V as in AD
2.	In the hippocampus, pretangles, NFTs or extracellular tangles preferentially affecting CA2 and pretangles and prominent proximal dendritic swellings in CA4. These regional p-tau pathologies differ from the preferential involvement of CA1 and subiculum found in AD
3.	Abnormal p-tau immunoreactive neuronal and astrocytic aggregates in subcortical nuclei, including the mammillary bodies and other hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum, and isodendritic core (nucleus basalis of Meynert, raphe nuclei, substantia nigra and locus coeruleus)
4.	p-Tau immunoreactive thorny astrocytes at the glial limitans most commonly found in the subpial and periventricular regions
5.	p-Tau immunoreactive large grain-like and dot-like structures (in addition to some threadlike neurites)
<i>Non-p-tau-related pathologies:</i>	
1.	Macroscopic features: disproportionate dilatation of the third ventricle, septal abnormalities, mammillary body atrophy, and contusions or other signs of previous traumatic injury
2.	TDP-43 immunoreactive neuronal cytoplasmic inclusions and dot-like structures in the hippocampus, anteromedial temporal cortex and amygdala

abnormal hyperphosphorylated tau in neurons and astroglia distributed around small blood vessels at the depths of the cortical sulci in an irregular pattern”. Other criteria were considered supportive but nonspecific. These, along with exclusionary criteria, are outlined above (Table 13.1).

McKee and colleagues reported the results of the consensus conference as a “first step towards the development of validated neuropathological criteria for CTE”, reflecting the need for prospective studies to fully understand this complicated disorder. One of the central controversies in CTE is the lack of brain-behavior relationship between the tau deposition and pre-death behavioral symptoms, and the presence of tau depositions in asymptomatic cognitively normal people with age. Also significant is the small number of cases described thus far, the lack of suitable control data (e.g., athletes exposed to TBI dying without symptoms, athletes with and without a history of steroid use, individuals who die of suicide or with depression who were not athletes, etc.). The causal link between the pathological findings described as CTE and the earlier experience of rTBI requires further study [31, 34, 35].

Clinical Criteria

CTE remains a research diagnosis, describable at autopsy. There are attempts at clinical criteria but they are based on data collected at literature review or retrospectively collected data (“psychological autopsies”) on small groups of pathologically-verified patients.

Jordan introduced criteria for “Chronic Traumatic Brain Injury of Boxing” (cTBI) which he considers synonymous with CTE, and refers to as the “cumulative, long-term neurological consequences of repetitive concussive and subconcussive blows to the brain” [36]. He presented criteria for probable, possible or improbable levels of the disorder, specific to boxers, and more likely in professional boxers. Probable cTBI required two or more neurological processes from a short list involving cerebellar dysfunction, pyramidal tract disease, or extrapyramidal disease and specifically these needed to be distinct from other diagnosable diseases. Possible TBI referred to any neurological syndrome that could be explained by another known neurological disease such as AD or Parkinson’s. He labelled patients as improbable cTBI if they had a neurological disease and a neurologic process distinct from those symptoms described under probable. He also devised a nine-point chronic brain injury scale with three points given for each of motor, cognitive and behavioral syndromes depending on severity.

Victoroff suggested criteria based on review of the literature, broken down into clinically probable or possible with either acute or delayed onset. Their criteria are designated as research criteria with a need for empirical definition [33].

Most recently, researchers led by Dr. Bob Stern at Boston University have collected “psychological autopsy data, which involves detailed interviews of the loved ones of individuals who come to autopsy. The results of which have led to the suggestion that there are two broad cognitive phenotypes, one presenting with behavior/mood changes, the other with cognitive changes [14]. The behavioral patients tended to present at a younger age, while the cognitive patients presented older. However, conclusions were drawn from only 33 patients, and the group acknowledges that the data remain preliminary. The same group has established a set of criteria for what they call “Traumatic Encephalopathy Syndrome” [37], also stipulated as a set of research criteria, not yet ready for clinical use. These are outlined below. Unlike Victoroff, they did not exclude cases that could not otherwise be accounted for by another known disorder, but rather allow for comorbidity (Table 13.2).

These research criteria have invited criticism: In a recent review article, Iverson [35] wrote “this syndrome is extraordinarily broad in scope, encompassing people with mild depression and those with late-stage dementia. For example, if a person played high school and collegiate sports (for at least 2 years at the collegiate level) and has current problems with depression, anxiety and headaches, that person would meet criteria for the new Traumatic Encephalopathy Syndrome” (p. 277). In addition to this concern, it should be noted that the clinical criteria overlap greatly with frontotemporal dementia, another neurodegenerative disease that disproportionately affects younger men and is often caused by underlying tauopathy. It seems questionable to re-diagnose FTD patients with CTE based solely on a very remote history of head injury. Thus, continued attention to the clinical presentation of CTE is required, and will be delivered by studies which are currently underway.

Suicide is a behavior that has become associated with CTE, perhaps mainly due to media reports of high profile sports stars such as Junior Seau and Jovan Belcher who committed suicide and were found to have CTE at post mortem. The evidence

Table 13.2 Research criteria for traumatic encephalopathy syndrome (TES)

General criteria for traumatic encephalopathy syndrome (Montenigro et al., 2014)	
All five criteria must be met for a diagnosis of TES:	
1.	History of multiple impacts to the head (or to the body resulting in impulsive force transmitted to the head). Multiple impacts are defined based upon (a) the types of injuries and (b) the source of exposure
	(a) Types of injuries:
i.	Mild TBI or concussion, defined according to the Zurich 2012 Consensus Statement on Concussion in Sport as a ‘complex pathophysiological process affecting the brain, induced by biomechanical forces...caused either by a direct blow to the head, face, neck or elsewhere on the body with an “impulsive” force transmitted to the head...the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies. Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness. History of this form of trauma can be based on documented records from health-care providers or on self- or informant-reports, after being given an appropriate definition of ‘concussion’. If there is no reported exposure to other repetitive hits to the head, there should be a minimum of four documented mild TBIs or concussions
ii.	‘Subconcussive’ trauma, defined as biomechanical force to the head or body similar to, or less than, that required for symptomatic concussion but without symptoms and clinical presentation consistent with concussion
	(b) Source of exposures:
i.	Involvement in ‘high exposure’ contact sports (including, but not limited to, boxing, American football, ice hockey, lacrosse, rugby, wrestling, and soccer) for a minimum of 6 years, including at least 2 years at the college level (or equivalent) or higher
ii.	Military service (including, but not limited to, combat exposure to blast and other explosions as well as non-combat exposure to explosives or to combatant or breach training)
iii.	History of any other significant exposure to repetitive hits to the head (including, but not limited to, domestic abuse, head banging, and vocational activities such as door breaching by police)
iv.	For moderate/severe TBI, any activity resulting in the injury (for example, motor vehicle accident)
2.	No other neurological disorder (including chronic residual symptoms from a single TBI or persistent post-concussion syndrome) that likely accounts for all clinical features, although concomitant diagnoses of substance abuse, post-traumatic stress disorder (PTSD), mood/anxiety disorders, or other neurodegenerative diseases (for example, AD and frontotemporal dementia) or a combination of these can be present
3.	Clinical features must be present for a minimum of 12 months. However, if treatment (for example, ‘antidepressant’ medication) results in an improvement in select symptoms, the clinician should use her or his best judgment to decide whether the symptoms would have persisted or progressed if treatment had not been initiated
4.	At least one of the core clinical features must be present and should be considered a change from baseline functioning
5.	At least two supportive features must be present
Core clinical features of traumatic encephalopathy syndrome	
At least one of the core clinical features must be present:	

(continued)

Table 13.2 (continued)

1. <i>Cognitive</i> . Difficulties in cognition:
(a) As reported by self or informant, by history of treatment, or by clinician's report of decline; and
(b) Substantiated by impairment on standardized mental status or neuropsychological tests of episodic memory, executive function, and/or attention, as defined by scores at a level of at least 1.5 standard deviations below appropriate norms
2. <i>Behavioral</i> . Being described as emotionally explosive (for example, having a 'short fuse' or being 'out of control'), physically violent, and/or verbally violent, as reported by self or informant, by history of treatment, or by clinician's report. A formal diagnosis of intermittent explosive disorder would meet this criterion but is not necessary
3. <i>Mood</i> . Feeling overly sad, depressed, and/or hopeless, as reported by self or informant, by history of treatment, or by clinician's report. A formal diagnosis of major depressive disorder or persistent depressive disorder would meet this criterion but is not necessary
Supportive features of traumatic encephalopathy syndrome
A minimum of two of the following features must be present for a diagnosis of TES:
1. <i>Impulsivity</i> . Impaired impulse control, as demonstrated by new behaviors, such as excessive gambling, increased or unusual sexual activity, substance abuse, excessive shopping or unusual purchases, or similar activities
2. <i>Anxiety</i> . History of anxious mood, agitation, excessive fears, or obsessive or compulsive behavior (or both), as reported by self or informant, history of treatment, or clinician's report. A formal diagnosis of anxiety disorder would meet this criterion but is not necessary
3. <i>Apathy</i> . Loss of interest in usual activities, loss of motivation and emotions, and/or reduction of voluntary, goal-directed behaviors, as reported by self or informant, history of treatment, or clinician's report
4. <i>Paranoia</i> . Delusional beliefs of suspicion, persecution, and/or unwarranted jealousy
5. <i>Suicidality</i> . History of suicidal thoughts or attempts, as reported by self or informant, history of treatment, or clinician's report
6. <i>Headache</i> . Significant and chronic headache with at least one episode per month for a minimum of 6 months
7. <i>Motor signs</i> . Dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other features of parkinsonism. If present, the modifier 'with motor features' should be used (see below)
8. <i>Documented decline</i> . Progressive decline in function and/or a progression in symptoms and/or signs, based upon repeated formal testing, clinician examination, or other formal measurement (for example, informant questionnaire) for a minimum of 1 year
9. <i>Delayed onset</i> . Delayed onset of clinical features after significant head impact exposure, usually at least 2 years and in many cases several years after the period of maximal exposure. It should be noted, however, that individual cases may begin to develop the clinical features of TES during their period of head impact exposure (for example, while still actively involved in a collision sport), especially older individuals or those who have been engaged in the high-exposure activity for many years. It may also be difficult to differentiate the clinical presentation of prolonged or persistent post-concussion syndrome (pPCS) from that of TES. Therefore, there could be cases for whom there is overlap of resolving pPCS and the initial features of TES, thus masking any delayed onset of TES
Traumatic encephalopathy syndrome diagnostic subtypes
1. TES behavioral/mood variant (TES-BMv)
(a) <i>Behavioral</i> or mood core features (or both) without cognitive core features

Table 13.2 (continued)

2. TES cognitive variant (TES-COGv)
(a) Cognitive core features without behavioral or mood core features (or both)
3. TES mixed variant (TES-MIXv)
Both cognitive core features and behavioral or mood core features (or both)
4. TES dementia (TES-D)
(a) Progressive course of cognitive core features with or without behavioral or mood core features (or both)
(b) Evidence of ‘functional impairment’, defined as cognitive impairment (or cognitive impairment exacerbated by behavioral or mood impairment or both) that is severe enough to interfere with the ability to function independently at work or in usual activities, including hobbies, and instrumental activities of daily living. The determination of functional impairment is based on clinician’s judgment, taking into account informant reports as well as consideration of individual differences with regard to level of expected responsibility and daily challenges
(c) If the clinical presentation is not distinguishable from that of dementia due to AD or another neurodegenerative disease (for example, frontotemporal dementia), both diagnoses may be given, either with one being ‘primary’ and the other being ‘secondary’ or with the term ‘mixed’ used if neither is presumed primary

published to date suggests that NFL retirees are less likely to die by suicide than other men their age [38]. However, depression has been cited as a potential clinical symptom of CTE, thus suicidality is possible and should always be discussed with patients in clinic, regardless of the potential diagnosis.

No prospective studies have yet been completed to assist in establishing a causal link between CTE pathology and a clinical syndrome. While such studies are underway (e.g., a recent study funded by U01, The DIAGNOSE-CTE Research Project in which SJB, author of this chapter, and JLC, editor of this book, are investigators) results involving sufficient numbers to draw reliable conclusions remain several years away.

Further complication comes from litigation, both current and future, of which many of the athletes involved in studies on the long term impact of TBE are a part. It is known that litigants behave differently, as a group, on cognitive tests compared with non-litigants [39, 40]. There is motivation to do poorly, as decisions on compensation relate to diagnosis but also severity. Even in a research setting, this needs to be taken into account and will likely complicate the understanding of true cognitive impact of sport related TBI.

Epidemiology of CTE

While there are no prospective epidemiological studies in CTE, the pathologically confirmed cases so far have been overwhelmingly male, aged from 17 to 98 years and mostly in sports, but also military and in one case a clown with a history of head injury [41]. No conclusions can yet be drawn on prevalence or incidence rates.

Approach to Suspected CTE

Diagnosis of CTE is complex and uncertain. CTE, at this stage, might be added to a differential during life but definitive diagnosis is impossible. Getting patients and their families involved in research studies will result in better understanding of the syndrome and its underlying pathology. Sending brains to a pathologist for autopsy and collecting more information is critical to the refinement of both pathological and clinical diagnostic criteria. Including patients and their families in research will also be important. At this stage treatment for CTE does not exist, but treatment for symptoms, or alternative diagnoses such as depression, which may respond well to treatment, is possible. Furthermore, support groups for similar syndromes such as frontotemporal dementias exist and may be of great use to family members. Presumptive misdiagnosis has occurred, for example in the case of Todd Ewen (<https://www.washingtonpost.com/news/early-lead/wp/2016/02/11/former-nhl-enforcer-todd-ewen-who-committed-suicide-found-to-not-have-cte/>). This information may have contributed to this individual making the drastic decision to end his life. This, of course, is to be avoided where possible. Thus, treating the symptoms, as with any degenerative disease, is paramount, as is keeping an open mind to alternative underlying disorders. Figure 13.1 outlines the steps that could be taken if you suspect CTE in a patient. To date, there are no clinical diagnostic criteria for CTE.

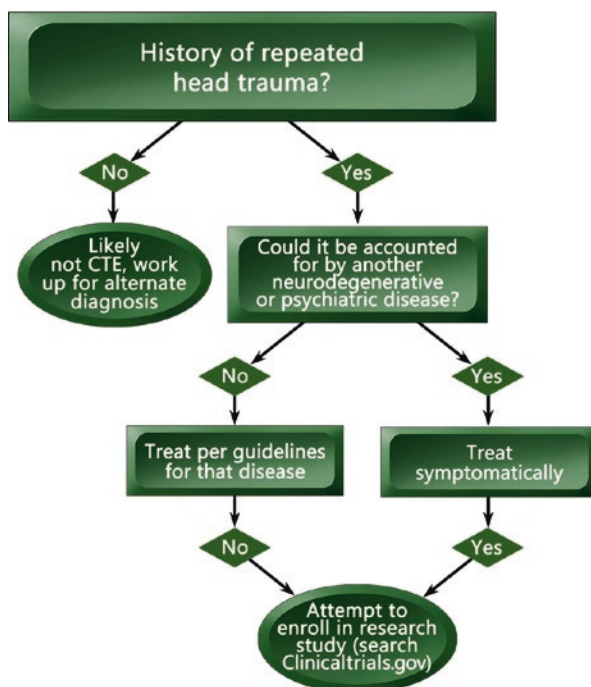


Fig. 13.1 Supportive features of CTE pathology agreed upon by NINDS/NBIB consensus (2013)

ICD-10 Codes

F07.81 Postconcussional syndrome, or codes associated with neurodegenerative or mood disorders if they meet criteria or are being ruled out.

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Chapter 14

Prion Disorders

Ethan Gore and Brian S. Appleby

Clinical Pearls

- There are several different clinical phenotypes of prion disease aside from classical Creutzfeldt-Jakob disease, which is usually characterized by dementia, ataxia, and myoclonus.
- There are three different etiologies of prion disease: sporadic (85%), genetic (10–15%), and acquired (<1%).
- Pre-morbid diagnosis of probable prion disease is achieved by recognizing the clinical syndrome in addition to suggestive diagnostic tests such as EEG (periodic sharp wave complexes), CSF markers (14-3-3, tau, and RT-QuIC), and brain MRI (hyperintensity in the basal ganglia and/or cortical gyri).

Introduction

Prion diseases are caused by an abnormal conformer of the prion protein (PrP^{Sc}). The PrP^{Sc} isoform differs from the normal prion protein (PrP^C) in that it is partially resistant to degradation by proteinase K and insoluble in non-denaturing detergents. PrP^{Sc} irreversibly converts nearby PrP^C to PrP^{Sc} resulting in self-propagation [1]. Accumulating PrP^{Sc} aggregates into amyloid plaques capable of spreading to adjacent cells and even to other hosts. PrP^{Sc} is called a prion because it is a

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pro-teinaceous *in*-fectious particle without nucleic acids [1]. The accumulation of prions causes prionopathies, which are characterized by severe progressive dementias that vary based on the prion strain, the prion protein gene (PRNP) sequence of the host, and route of inoculation if acquired. Prions cause neuronal apoptosis dependent upon microglial activation and the presence of PrP^c [2].

There are three etiologies of prion disease: sporadic, genetic, and acquired. The sporadic generation of PrP^{Sc} is not well understood, but sporadic prionopathies have been theorized to occur due to errors in protein synthesis between transcription and post-translation [3]. Some mutations within PRNP are known to inevitably result in the eventual *de novo* generation of genetic prion disease (i.e., genetic Creutzfeldt-Jakob disease (gCJD), fatal familial insomnia (FFI), and Gerstmann-Sträussler-Scheinker disease (GSS)). Lastly, PrP^{Sc} can be acquired from an outside source, where a cascade of conversion to PrP^{Sc} ensues. Acquired CJD may be iatrogenic from donated tissues or hormones that were infected with prions or from contaminated surgical instruments. Variant CJD (vCJD) is a type of acquired CJD contracted by the ingestion of prions from cattle infected with bovine spongiform encephalopathy.

Clinical Manifestations

With an incidence of one to two per million people, sporadic CJD (sCJD) accounts for 85% of all human prion disease with an average age of onset of 61 [4]. Most patients demonstrate a combination of symptoms including dementia, cerebellar or visual disturbance, myoclonus, pyramidal or extrapyramidal symptoms, and akinetic mutism. Seventy two percent of cases present with cognitive impairment, 44% present with ataxia, 26% with vertigo, and 35% with visual or oculomotor impairment. In terms of psychiatric symptoms, 28% present with a mood disorder, 23% with a behavior or personality change, 20% with psychosis or agitation, and 18% with a sleep disorder [5]. The average survival time is 4–6 months with very few surviving over 2 years.

To aid in the research and prognosis of a disease that may present and progress in varied ways, seven phenotypic variants of sCJD have been established [6]. Six variants of sCJD were designated based on three potential PRNP codon 129 genotypes and two recognized types of protease-resistant prion protein fragments found in brain tissue. The three codon 129 genotypes possible for each patient are MM, MV, and VV where M = methionine and V = valine [7]. For example, a case would be classified as MM1 if the patient's PRNP analysis revealed methionine-methionine at codon 129, and Western blot demonstrated the type 1 prion protein. A total of seven variants are recognized because the MM2 subtype has been divided into two separate variants: one called the thalamic variant, also called sporadic fatal insomnia, and the other called the cortical variant. Clinical, electrophysiological, and radiographic distinguishing features of the seven subtypes often allow pre-morbid classification of patients, which can aid in prognosis (Table 14.1) [8, 9].

Table 14.1 Characteristics of sporadic Creutzfeldt-Jakob disease (based on genetic and molecular features) [9–14]

	MM1	MV1	VV1	sFI or MM2 Thalamic	MM2 Cortical	MV2	VV2
Percentage of sCJD patients	65%	3%	1%	3%	3%	10%	15%
Clinical characteristics	Early myoclonus, dementia, Heidenhain variant	Early myoclonus, dementia	Progressive dementia	Insomnia, hyperactivity, ataxia, dementia	Progressive dementia	Ataxia and dementia at onset	Ataxia at onset, Oppenheimer-Brownell variant
Mean age in years at onset (range)	65 (42–91)	62.1 (51–72)	39.3 (24–79)	52.3 (13–71)	64.3 (49–77)	59.4 (40–81)	61.3 (41–80)
Duration in months (range)	3.9 (1–18)	4.9 (2–9)	15.3 (14–16)	15.7 (9–36)	15.6 (8–24)	17.1 (5–72)	6.5 (3–18)
EEG findings	80% have PSWCs	70% have PSWCs	No PSWCs	No PSWCs	No PSWCs	PSWCs in under 10%	PSWCs in under 10%
Protein 14-3-3 sensitivity	87%	94%	100%	Low	70%	57%	84%
Tau sensitivity	100%	94%	89%	Low	89%	69%	92%
DWI and FLAIR findings on MRI	Often caudate and putamen hyperintensities and widespread frontal, parietal, and cingulate cortical hyperintensities in half sparing the thalamus and hippocampus	Often caudate and putamen hyperintensities and frontal, parietal, and insular cortical hyperintensities typically involving the hippocampus	Rare caudate, putamen, or thalamic hyperintensities and often cingulate, insular, and temporal hyperintensities	No FLAIR or DWI hyperintensities usually seen in other subtypes of sCJD. Perfusion imaging shows decreased thalamic perfusion	Widespread cortical hyperintensities often involving lobes with rare caudate, putamen; thalamic and cerebellar hyperintensities possible	Prominent caudate, putamen, and thalamus hyperintensities with limited cortical hyperintensities usually restricted to the frontal and cingulate cortices	Predominant caudate and putamen hyperintensities and also hyperintensities in the thalamus and cingulate

Mutations in the PRNP gene cause about 15% of human prion disease. Over 30 mutations in PRNP that result in prion disease have been described. Most are autosomal dominant with nearly complete penetrance by the ninth decade of life. In genetic prion disease, the mean age of onset is 56, and the average survival time is 14 months [4]. The most common genetic prion disease is gCJD, which may be caused by several different mutations. The clinical manifestations vary based on the mutation site. For example, the most common mutation in gCJD (E200K) is known for causing ataxia, myoclonus, and pyramidal signs, but the T183A mutation causes extrapyramidal symptoms [15]. Gerstmann-Sträussler-Scheinker disease (GSS) is caused by several mutations in PRNP that result in the GSS pathologic hallmark of multicentric amyloid plaques [16]. Patients with GSS typically seek medical attention for progressive cerebellar dysfunction and/or parkinsonism developing in middle age and do not develop dementia until late in the disease course. The average survival time in GSS is 5 years, ranging from 3 to 8 years [17].

The clinical manifestations of genetic prion disease do not differ based only on the mutation site but also based on the sequence of the rest of PRNP. For example, inheriting a D178N mutation with a valine at codon 129 of the same allele results in a gCJD phenotype with cognitive impairment, depression, and irritability, but inheriting an allele with the D178N mutation and a methionine at codon 129 of the mutated allele results in FFI. Defined by this specific haplotype, FFI is classified as a separate type of genetic prion disease due to its distinct presentation marked by progressive insomnia, sleep disorder, fatigue, autonomic instability, hypervigilance, pyramidal and extrapyramidal signs, myoclonus, and ataxia [4]. Onset is usually in midlife and spares cognition until late stages with average disease duration of over a year. The core neuropathologic finding of FFI is severe spongiform changes of the thalami.

Acquired prion diseases generally affect younger populations. Iatrogenic CJD (iCJD) has a mean age of onset of 43 years and an average survival time of 11 months and vCJD has a mean age of onset of 32 years and an average survival time of 13 months. Due to a better understanding of prion disease, the incidence of iCJD has declined tremendously in recent decades. Cadaver sourced human growth hormone (hGH) was administered from the 1950s to the 1980s when it was replaced by recombinant hGH [8]. Contaminated hGH has caused over 220 cases of iCJD with mostly cerebellar deficits and late stage dementia and a mean incubation time of 17 years [18]. Other human gonadotropin administrations besides hGH caused four other incidents of iCJD in Australia. Cadaveric dura mater transplants have caused over 225 cases of iCJD with an average incubation time of 12 years, but dural substitutes are now used to close large dural openings. Fewer than ten cases of iCJD from contaminated neurosurgical instruments including stereotactic EEG needles have been reported with an average incubation period of less than 2 years. There are two descriptions of iCJD following a corneal transplant from a donor with probable prion disease. Other cases of prion disease following corneal transplant exist but without a clear description of prion disease in the donor [19]. There have been four recognized cases of vCJD transmission via blood transfusion, but there has been no known blood-borne transmission of the other prion diseases [20].

In 1985, bovine spongiform encephalopathy (BSE) was first described as a prion disease affecting cattle and it was soon evident that BSE could be transmitted to other species [21]. The first report of vCJD occurred in 1996, and the next year vCJD was shown to be caused by BSE. At an average age of 32, clinical features usually begin with 6 months of psychiatric disturbances like depression, anxiety, and delusions or sensory symptoms followed by the rapid development of neurological problems like dementia, ataxia, chorea, dystonia, and myoclonus [22]. Survival after onset is 14 months on average.

Variant CJD has affected under 250 patients to date, nearly exclusively in Europe [21]. The incidence of BSE plummeted in the 1990s after feeding cow products to cows became illegal and after slaughtering millions of affected cattle. The number of deaths per year from vCJD peaked at 28 in 2000 and has gradually declined. The vast majority of vCJD cases have had a codon 129 MM genotype. A 2013 study of lymphoreticular tissue from 32,411 routine appendectomies in the UK showed PrP^{Sc} consistent with vCJD in 16, only half of whom had MM genotypes. PrP^{Sc} from an asymptomatic patient's spleen was shown to be transmissible to mice. The discrepancy between the prevalence of vCJD prions in lymphoreticular tissues and the relatively small number of patients who have developed vCJD clinical disease is not understood [23]. Asymptomatic carriers may eventually develop clinical disease and as well as be capable of disease transmission.

Diagnostic Approach

When prion disease is clinically suspected, several studies can be used to establish the likelihood of a prion disorder (Table 14.1) [10, 24]. The most important part of diagnosing prion disease is first ruling out other etiologies. The definitive diagnosis of any prion disorder requires a histological review of brain tissue. However, particular findings in electroencephalography, magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) may be suggestive of a prion disease. These findings vary based on disease etiology, molecular subtype, and illness duration.

Electroencephalography (EEG) in prion disease may show focal or diffuse slowing in the early stages, but in two thirds of sCJD, synchronous periodic sharp wave complexes (PSWCs) at a frequency of about one-half to two hertz eventually appear [25, 26]. Other causes of PSWCs include toxic and metabolic encephalopathies, Hashimoto's encephalopathy, and end stage Alzheimer's disease (AD) or dementia with Lewy bodies (DLB). The periodic sharp waves typical in sCJD are very rare in vCJD and only occur in about 10% of gCJD cases. In FFI, EEG shows a loss of sleep architecture including an absence of K complexes and sleep spindles.

Magnetic resonance imaging (MRI) can predict sCJD with over 90% sensitivity and specificity [27]. Sporadic CJD results in asymmetric diffusion weighted imaging (DWI) hyperintensity in the cortical ribbon, medial temporal lobes, caudate heads and putamina (Fig. 14.1). The vast majority of sCJD patients have high cortical DWI signal, and two-thirds have a high cortical signal plus high signal in the

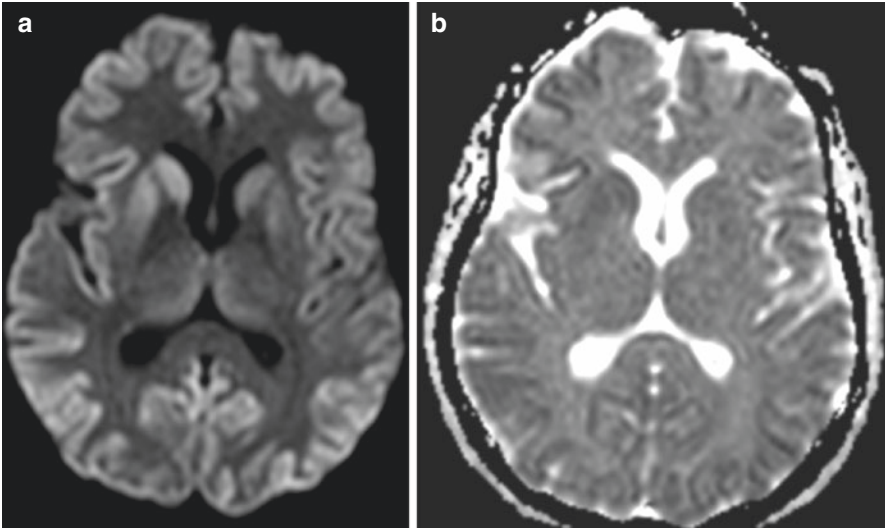


Fig. 14.1 (a) Brain diffusion weighted magnetic resonance imaging shows hyperintensities of the caudate heads and putamina greater on the right as well as hyperintensities of the right insular cortex and bilateral parietal, occipital, and posterior cingulate cortices. (b) Brain apparent diffusion coefficient (ADC) magnetic resonance imaging shows cortical hypointensity in many cortical regions that is most prominent in the right frontal cortex. In prion disease, cortical ADC hypointensity is more subtle and rare than caudate, putamen, and thalamic hypointensity

caudate and putamen. The DWI hyperintensity can often be confirmed to represent restricted diffusion on apparent diffusion coefficient (ADC) maps, especially if subcortical [28]. Fluid attenuated inversion recovery (FLAIR) hyperintensity is usually present but less evident in the same regions. In one series of non-prion rapidly progressive dementias (RPD) such as paraneoplastic limbic encephalitis, 9/29 cases had gray matter hyperintensity, but all were greater on FLAIR than DWI, and all had normal ADC intensity. For MRI patterns expected in the seven subtypes of sCJD, see Table 14.1 [29]. Unlike sCJD patients, over 90% of those with vCJD have symmetric FLAIR hyperintensity in the posterior thalami relative to the anterior putamina, the “pulvinar sign” [30]. Most of the FLAIR hyperintensity extends symmetrically to involve the regions of the dorsomedial thalamic nuclei, rendering the “hockey stick sign”. Because most vCJD cases occurred before DWI was widely available, the role of DWI in the diagnosis of vCJD is unclear. Brain MRI findings in GSS and gCJD may resemble those in sCJD but are highly variable and dependent upon the causative mutation. MRI in FFI only shows nonspecific abnormalities such as atrophy [31].

The direct measurement of two non-specific cerebrospinal fluid (CSF) markers of neurodegeneration, protein 14-3-3 and tau, can be used to aid in the pre-morbid prediction of sCJD. The 14-3-3 protein is found in neurons and glia and has many functions including the regulation of cell differentiation and proliferation [32]. It is elevated in the CSF when extensive rapid brain damage from any etiology occurs. The sensitivity of elevated protein 14-3-3 for sCJD generally ranges from 85 to 95%, but its specificity ranges widely from 47 to 97% [33, 34]. In vCJD, CSF 14-3-3 protein levels are often normal. Tau proteins stabilize microtubules, and a very high total tau (T-tau) level in the CSF typically indicates sCJD, but may indicate other causes of cerebral injury such as AD [35, 36]. Phosphorylated tau (P-tau) levels are often elevated in AD but not in sCJD. A high T-tau/P-tau ratio predicts sCJD with 75–95% sensitivity and 94–97% specificity. Protein 14-3-3 and tau sensitivities vary by mutation in genetic prion diseases, and are particularly low in FFI and GSS [10].

Real time quaking induced conversion (RT-QuIC) is a relatively new laboratory test for sCJD with a sensitivity of 80–94% and a very high specificity of 98–100% [24, 37]. As a substrate, RT-QuIC uses recombinant PrP^c, and as an indicator, it uses the fluorescence of thioflavin T (ThT). A specimen, usually CSF, from a patient is added to the substrate and ThT, and the combination is shaken for 48 h. If the specimen contains PrP^{Sc}, conversion of the substrate to PrP^{Sc} and aggregation of PrP^{Sc} into plaques ensues. In the presence of the amyloid plaques, ThT displays enhanced fluorescence and a red shift of its emission spectrum that can be monitored in real time. RT-QuIC is the first antemortem disease specific biomarker for prion disease aside from brain biopsy and is currently being extensively studied. Brain biopsy is considered the gold standard for the ante mortem diagnosis of sCJD, but it results in significant morbidity, patient decompensation, high financial cost, and only about a 50% diagnostic rate in rapidly progressive dementia (RPD). Because there is no current treatment for prion diseases, should less invasive testing point to sCJD; a confirmatory brain biopsy would probably not alter patient treatment. A brain biopsy in RPD should only be considered when prion disease seems unlikely [38].

For cases of suspected prion diseases, various resources are available through the National Prion Disease Pathology Surveillance Center (NPDPS). The NPDPS provides CSF testing for protein 14-3-3, tau, and RT-QuIC, and it also receives all biopsy and autopsy tissues from suspected prion disease cases in the United States through a CDC funded Autopsy Program. The NPDPS can also perform genetic testing on brain tissue or blood specimens and has a brain MRI consultation program. Resources for families and professionals can be found at the NPDPS website, <http://case.edu/med/pathology/centers/npdpssc/>.

Figure 14.2 provides a guide to the diagnosis of RPD.

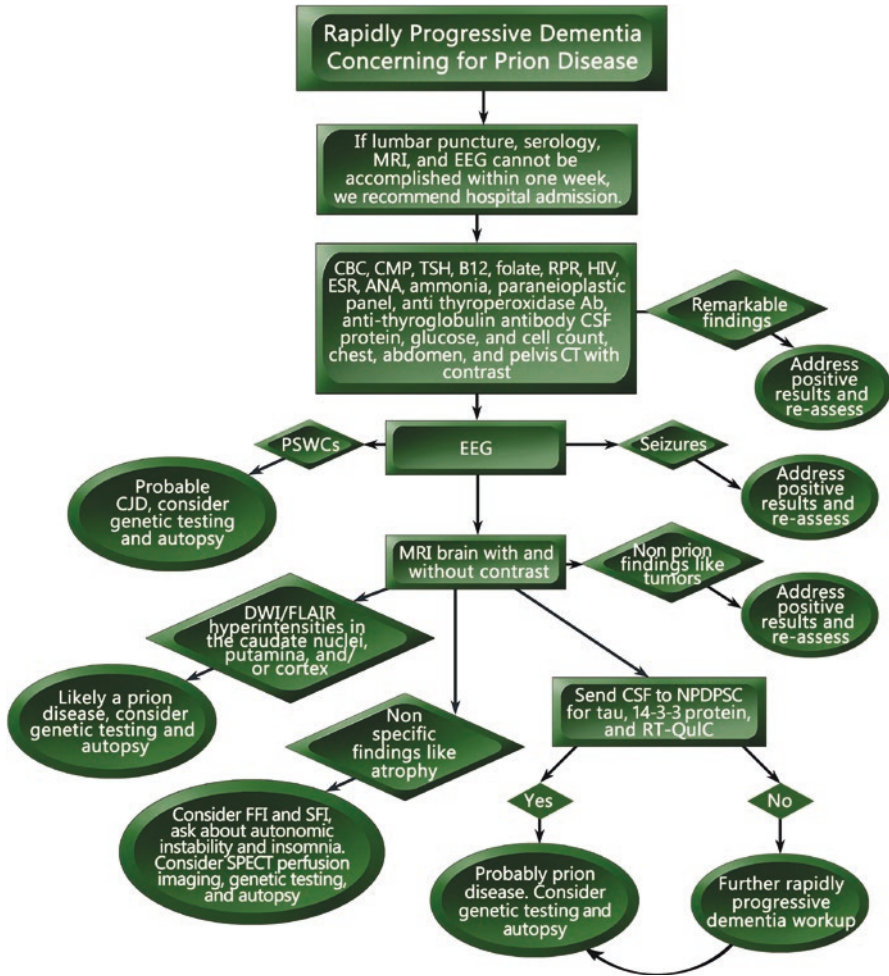


Fig. 14.2 Approach to the diagnosis of rapidly progressive dementia

Diagnostic Criteria

In 1998, the World Health Organization published official diagnostic criteria for the diagnosis of sCJD [25]. In 2009, MRI criteria were added in an update [39] (Table 14.2). These updated criteria do not incorporate CSF tau or RT-QuIC analysis. Definite diagnosis of sCJD requires a histological examination of brain tissue revealing spongiform change in gray matter or PrP^{Sc} immunoreactivity. Based on the 2009 criteria, possible sCJD can be diagnosed in a patient with dementia if at least two of four clinical signs appear within 2 years: myoclonus, cerebellar/visual

Table 14.2 Diagnostic criteria for sporadic Creutzfeldt-Jakob disease

Possible	Progressive dementia with duration under 2 years and
	At least two out of four of the following features:
	• Myoclonus
	• Visual or cerebellar disturbance
	• Pyramidal/extrapyramidal dysfunction
	• Akinetic mutism
Probable	Meets criteria for possible sCJD but without time constraints and
	At least one of the following signs:
	• PSWCs on EEG
	• A positive 14-3-3 CSF assay and a clinical duration to death <2 years
	• High FLAIR or DWI signal in the caudate nucleus and putamen and/or at least two cortical regions (temporal, parietal, occipital)
Definite	Brain tissue consistent with sCJD based on neuropathological examination, immunocytochemistry, Western blot for protease resistant prion protein, or the presence of scrapie-associated fibrils

deficits, pyramidal/extrapyramidal signs, or akinetic mutism. The diagnosis of probable sCJD makes no chronological stipulations but does require at least two out of the four clinical signs plus one or more of three positive test results. The first test result is PSWCs on EEG, and the second, which only applies if the duration is under 2 years, is an elevated CSF protein 14-3-3. The third test result is MRI DWI or FLAIR hyperintensity in the caudate nucleus and putamen and/or in at least two cortical regions (temporal, parietal, or occipital).

The diagnosis of gCJD requires definite or probable sCJD criteria plus definite or probable sCJD in a first-degree relative or the presence of a *PRNP* mutation. A GSS diagnosis can similarly be made based on disease specific mutations or based on multicentric PrP^{Sc} amyloid plaques found in the brain of the symptomatic patient or his/her primary relative. A *PRNP* mutation at codon 178 in cis with methionine at codon 129 in a symptomatic patient or in the symptomatic patient's first-degree relative is needed to diagnose FFI.

The diagnosis of iCJD can be made in the same way as sCJD but requires a recognized exposure risk. Iatrogenic CJD can also be diagnosed in patients with a progressive cerebellar syndrome who received human cadaveric pituitary hormone.

The rigorous criteria for vCJD have not changed since 1998. Patients must have no potential iatrogenic exposure, a clinical duration under 6 months, an age under 50 years, no PRNP mutation, no PSWCs on EEG, no alternative diagnosis after routine investigation, and MRI hyperintensity of the pulvinar nucleus on T2 or proton density weighted images. In addition, five of the following six symptoms must be present: early psychiatric conditions, early persistent paresthesia or dysesthesia, ataxia, chorea/dystonia or myoclonus, dementia, or akinetic mutism. In vCJD only, diagnosis may be further aided by detecting PrP^{Sc} in tonsillar biopsy tissue.

Differential Diagnosis

The most common clinical imitators of prion disease are degenerative diseases such as AD, DLB, frontotemporal dementia (FTD), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP). These diseases should not have the MRI findings typical in sCJD and vCJD. Vascular dementia (VaD) may also mimic CJD but should have evidence of cerebral hemorrhage or infarctions in vascular territories on MRI. Out of 1106 autopsies of patients suspected of having sCJD, 71 were found to have potentially treatable dementia etiologies [40]. Twenty-six had immune disorders like primary central nervous system (CNS) vasculitis, acute disseminated encephalomyelitis, limbic encephalitis, neurosarcoidosis, paraneoplastic syndrome, or Wegener's granulomatosis. Twenty-five had neoplastic disorders that were widely infiltrative without clear mass lesions like primary CNS lymphoma, angiotrophic lymphoma, leptomenigeal lymphoma, malignant glioma, or leptomenigeal carcinomatosis. Fourteen had infections like coccidioides, aspergillus, cryptococcus, roundworms, or eosinophilia without demonstrable parasites. Six had a metabolic disorder like Wernicke's encephalopathy. Other metabolic, toxic, and medication-induced encephalopathies should also be considered. Especially in young patients, congenital etiologies of dementia should be considered. In summary, the most important differential diagnoses of prion disease are potentially treatable conditions that may mimic prion disease.

Treatment

There is no approved treatment for prion disease, and it is unfortunately universally fatal. Several investigational treatments have undergone clinical trials (quinacrine, pentosan polysulphate, and doxycycline) that did not affect survival time. Management of patients with prion disease is aimed at alleviating symptoms and supporting the patient and his/her family. We strongly recommend referral to hospice once the diagnosis of prion disease is made to assist with end-of-life care and family support. We also recommend referral to support organizations that may assist in supporting the family (CJD Foundation, www.cjdfoundation.org and Alzheimer's Association, www.alz.org). Management of symptoms is similar to other neuro-geriatric conditions. Generally, behavioral and environmental modifications are tried first, and then, if necessary, pharmacotherapy is started at a low dose and slowly titrated upwards to alleviate symptoms. Some suggested treatments for various neuropsychiatric symptoms are listed in Table 14.3 and are presented in Chap. 23 on the management of neuropsychiatric symptoms in neurodegenerative disorders. Figure 14.3 provides an overview of management strategies.

Table 14.3 Management suggestions for prion disease

Symptom	Management options
Myoclonus	Nonpharmacologic: minimize stimulation
	Pharmacologic: clonazepam, levetiracetam, piracetam, valproic acid, topiramate, lamotrigine, zonisamide
Psychosis/agitation	Nonpharmacologic: address pain, hunger, constipation, and other needs, art, music, and aroma therapy
	Pharmacologic: quetiapine, risperidone, SSRIs, SNRIs, benzodiazepines
Depression/anxiety	Nonpharmacologic: art, music, and aroma therapy
	Pharmacologic: SSRIs, SNRIs, benzodiazepines
Sleep disorders	Nonpharmacologic: institute good sleep hygiene, minimize stimulation
	Pharmacologic: melatonin, trazodone, benzodiazepines
Constipation	Nonpharmacologic: frequent toileting, adequate oral hydration
	Pharmacologic: docusate, senna, fiber supplements
Dysphagia/rumination	Nonpharmacologic: thickener, cueing, different food textures
Seizures	Pharmacologic: levetiracetam, valproic acid, lamotrigine, lacosamide

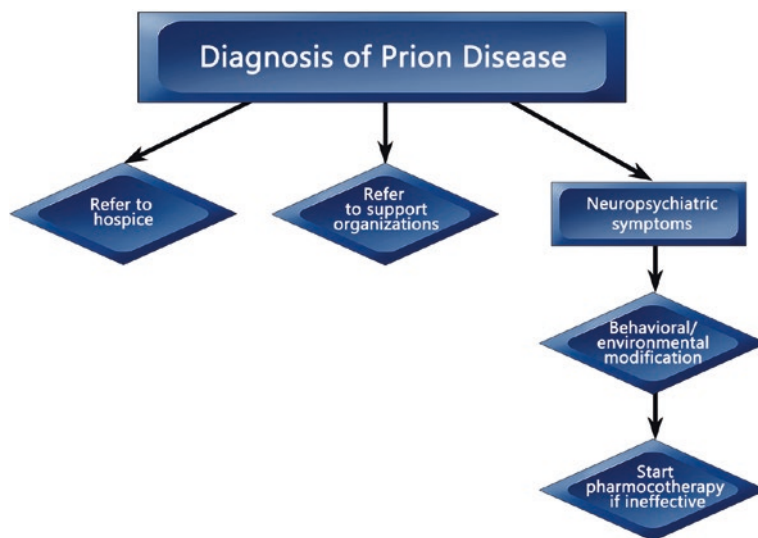


Fig. 14.3 Approaches to management of Creutzfeldt-Jakob disease

Prion Disorder ICD-10 Codes

Creutzfeldt-Jakob disease	A81.00
Sporadic Creutzfeldt-Jakob disease	A81.01
Other Creutzfeldt-Jakob disease	A81.09
Gerstmann-Straussler-Scheinker syndrome	A81.82
Fatal familial insomnia	A81.83

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Chapter 15

Neuromuscular Junction Disorders and Myopathies

Kathy Chuang and Mohammad Kian Salajegheh

Clinical Pearls

- Fluctuating weakness, in particular if worsened by activity and improved with rest and involving ocular/bulbar muscles, is most suggestive of myasthenia gravis.
- Fluctuating weakness that is predominantly found in the lower extremities in the elderly and accompanied by autonomic symptoms (orthostatic hypotension, dry eyes and mouth, early satiety and so forth) and reduced deep tendon reflexes, should raise suspicion for Lambert-Eaton myasthenic syndrome.
- Slowly progressive, asymmetric weakness and atrophy of the deep finger flexors (which flex the tips of the fingers) and knee extensors in the elderly, and to a lesser degree, weakness of elbow flexors/extensors and ankle dorsi-flexors, with relative sparing of shoulder abductors and hip flexors, should suggest the possibility of inclusion body myositis.

Introduction

Weakness, as a general term, is a common complaint of elderly clinic patients, and its evaluation may prove to be frustrating as it may be the presenting symptom in many conditions that may not be neurologic or even accompanied by true muscle weakness. Weakness should be clearly differentiated from “fatigue,” where a patient may lack the energy to start or continue on with a task, albeit having the strength to

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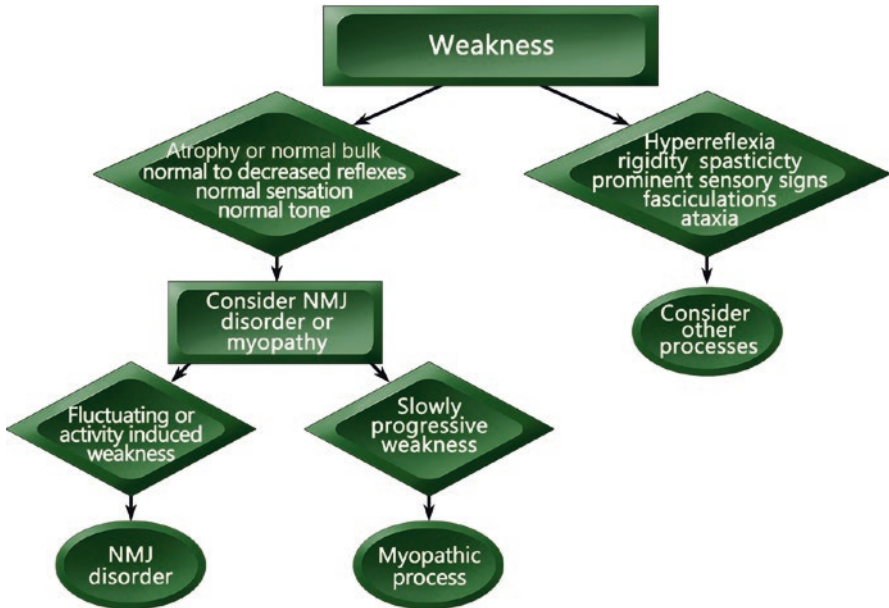


Fig. 15.1 Diagnostic care path for weakness. *NMJ* neuromuscular junction

do it, lack of “motivation” and “stamina,” restriction in the movement of joints from a rheumatologic condition as well as muscle spasticity and rigidity. On the other hand, a patient with weakness may present with other symptoms and complaints, including gait instability, falls, dysphagia, dysarthria, dyspnea, stooped posture, blurred vision and failure to thrive.

True weakness may stem from both central nervous system (CNS) (brain or spinal cord) and peripheral nervous system (PNS) disorders. In the PNS, while patients with involvement at the root and peripheral nerve level may primarily, or predominantly, present with weakness, they usually have sensory changes and other findings that would help correct localization. Pure weakness in the PNS is usually related to disorders of the motor neuron, neuromuscular junction or muscle (Fig. 15.1). In exploring the various etiologies leading to weakness, one should also consider deconditioning and disuse as well as normal aging (also known as “sarcopenia of aging”). In this chapter, we will focus on common NMJ and myopathic causes of weakness in the elderly, and on their presentation, diagnosis and management.

Neuromuscular Junction Disorders

Myasthenia Gravis

Myasthenia gravis (MG) presents in a bimodal distribution, with men demonstrating annual peak incidences between 30–34 and 70–74 years of age and women between 20–24 and 70–75 years of age. Its prevalence is estimated to be between 25

and 142 per million [1], and recent studies have suggested that there is an increasing incidence of MG in elderly patients, particularly in men [2].

Clinical Manifestations

The key clinical feature in myasthenia gravis is *painless, fluctuating weakness of the skeletal muscles*, over the course of minutes to days, often worsening as the day progresses. Interestingly, the pattern and intensity of weakness varies from person to person—it may be generalized, focal or multifocal, and mild to severe. Because MG may present in a focal fashion, it is not uncommon for patients to present to the emergency room worried about having an acute stroke. Most frequently, patients present with ocular and bulbar symptoms—ptosis, diplopia, dysarthria, dysphagia, and difficulty chewing. Ventilatory and limb muscles may also be involved. Overall it seems as though the ocular or bulbar forms are more frequent in the elderly, and only about 50% of elderly patients with ocular myasthenia will develop generalized myasthenia within 2 years [2].

Weakness may be exacerbated by warm temperatures, infection, stress, certain medications, hyper- and hypothyroidism, and can often be brought out by exercise. If a diagnosis of MG is suspected, physical examination should include maneuvers to fatigue muscle in order to elicit weakness—for example, looking for increasing ptosis or ocular misalignment after sustained upgaze for 1 min, or testing bilateral arm abduction strength, and then performing 30 repetitive arm abductions on one arm, followed by repeat testing of bilateral arm abduction strength, which should demonstrate weakness in the exercised arm. As cold temperatures may improve muscle strength, an ice-pack test can be performed—an ice pack is placed on a ptotic eyelid, and the cold temperature may improve the degree of ptosis. Other physical exam findings of importance include: (1) the frontalis sign - sustained contraction of the frontalis muscle to compensate for ptosis, (2) Cogan's lid twitch—the patient is asked to sustain downgaze for a few seconds, and then to saccade back to primary position by looking back up at the examiner's finger—a positive sign refers to a brief overshoot of the upper lid, resulting in scleral exposure between the limbus and the upper lid followed by return of ptosis, (3) ophthalmoplegia, (4) weakness of facial and jaw muscles—for example, weakness of eye closure against resistance, weakness of lip closure with holding of cheek puff against resistance, or weakness of jaw closure or opening, (5) tongue weakness against resistance, (6) palatal, lingual or nasal dysarthria, (7) weakness of ventilation—the patient may count out loud for as long as they can after a deep breath to estimate vital capacity—each number represents approximately 100 cc of vital capacity (counting to less than 20 is worrisome, where intubation is recommended with a forced vital capacity of <15 mL/kg) (8) weakness of neck flexion/extension, and (9) limb weakness. Sensory, visual field, and coordination testing should be normal, and generally, muscle bulk, tone and reflexes are preserved, unless there is severe weakness.

Patients with MG have a higher incidence of neoplastic and autoimmune diseases. MG is most commonly associated with thymic hyperplasia and thymomas. Thymomas themselves have been associated with other neurological disorders, such as Isaac's syndrome, rippling muscle disease, limbic and cerebellar encephalitis,

granulomatous myositis and autonomic neuropathy. Patients with MG are also more likely to have rheumatoid arthritis, systemic lupus erythematosus, Sjogren’s syndrome, red blood cell aplasia, ulcerative colitis, sarcoid, Addison disease and hyper- and hypothyroidism. Thus, history taking in patients with MG should include a review of systems to rule out other symptoms of neoplastic or rheumatologic disease.

Diagnostic Approach

Diagnosis of MG can be made through pharmacological, serological or electrodiagnostic testing (Fig. 15.2). Pharmacologic testing is usually performed with edrophonium testing (Tensilon test). Side effects of edrophonium testing include significant cholinergic effects, such as nausea, vomiting, and syncope due to transient heart block. After establishing a baseline degree of ptosis or ophthalmoparesis is noted. A butterfly needle or IV is inserted, and initially a 2 mg test dose of edrophonium is given. If there is no response after 30 s (i.e. no objective improvement of the ptosis or ophthalmoparesis) then 2 mg doses are administered every 10–15 s until a maximum dose of 10 mg is reached. The test is concluded when there is objective improvement, severe side effects, or maximum dose is reached. Atropine sulfate, an EKG machine and staff able to perform cardiac resuscitation should be available when this test is administered. Edrophonium testing is now

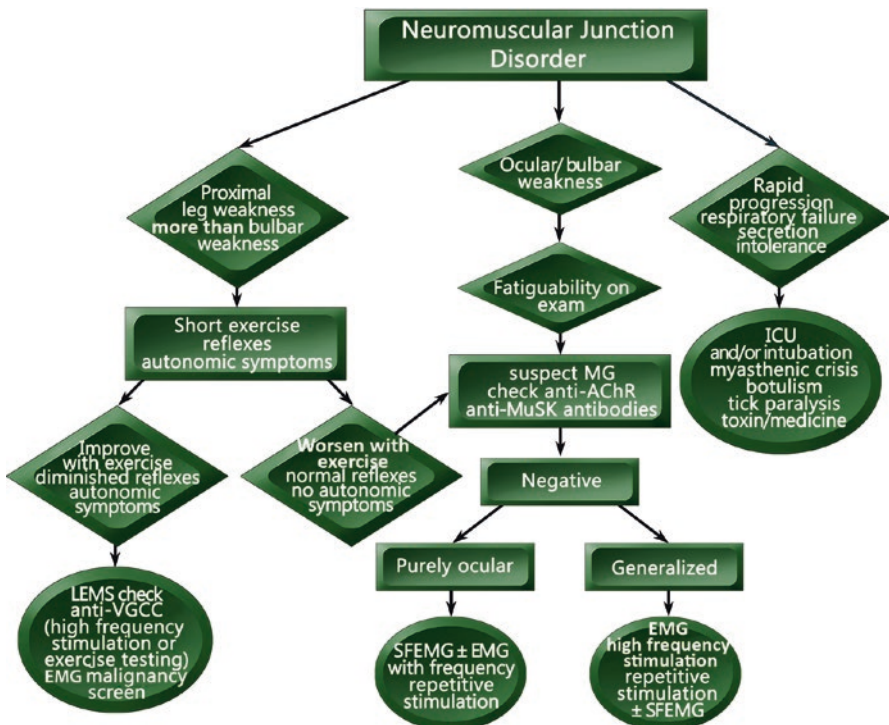


Fig. 15.2 Diagnostic care path for neuromuscular junction disorder

used less frequently than in the past due to false negative and false positive results, the possibility of adverse events, and the advent of serological testing [1, 3].

Laboratory

Patients may be tested for acetylcholine receptor (AChR) binding, blocking and modulating antibodies, as well as muscle specific tyrosine kinase (MuSK) antibodies. AChR antibodies occur in approximately 50–70% of patients with ocular myasthenia and between 70 and 90% of patients with generalized myasthenia. MuSK antibodies are positive in 39–70% of patients who are AChR antibody negative. Antibody titers do not correlate with the severity of the disease, and may be negative at the onset of disease, possibly requiring repeat testing months later. The presence of AChR binding and modulating antibodies or MuSK antibodies, in the setting of a clinical context consistent with MG, confirms a diagnosis of MG. AChR blocking antibodies are only very rarely found in the absence of AChR binding antibodies, and have no clinical utility. AChR modulating antibodies are often found in high titers in the presence of thymoma. Anti-striational muscle antibodies are not useful for diagnosis of MG. While their presence in MG patients less than 40 years may be associated with thymoma, this is not the case in older patients. Thyroid stimulating hormone (TSH) should also be evaluated, given a predisposition to autoimmune thyroid disease, and the possibility for Graves' ophthalmoplegia for those with pure ocular symptoms [2].

Electrophysiology

Electrophysiologic testing with slow frequency (2–3 Hz) repetitive nerve stimulation (RNS) can confirm the presence of a neuromuscular junction disorder, with a diagnostic yield of 45–99%, depending on how severe and generalized the weakness is. Single fiber EMG (SFEMG) has the highest sensitivity of all testing modalities, with a yield between 59 and 99%; however, it is less specific [1, 3]. Given this, in patients with negative serologic testing, slow frequency RNS can be considered for patients with clinical suspicion for myasthenia, followed by SFEMG, in patients who have a non-diagnostic test.

Imaging

All patients with a diagnosis of MG should have CT or MRI of the chest to exclude thymoma.

Other Ancillary Tests

In patients with suspected respiratory compromise or dysphagia, pulmonary function test and modified barium swallow, with the appropriate referrals should be considered, respectively.

Therapy

Treatment for MG depends primarily on the severity of the disease, as well as the presence of thymoma and comorbid medical conditions (Fig. 15.3). Patients in myasthenic crisis, with severe bulbar symptoms or respiratory compromise, should be admitted for close monitoring in an intensive care unit. Intubation is suggested for patients with forced vital capacity <15 mL/kg or negative inspiratory pressure <30 cmH₂O. Intravenous immunoglobulin (IVIG) 2 g/kg over 5 days or plasmapheresis every other day for up to 2 weeks is started for acute management. However, during this time, a bridge to long-term treatment is often needed—high dose steroids (intravenous methylprednisolone 1 g/day for 3–5 days followed by prednisone 60 mg daily, or prednisone 60 mg daily from the beginning) are often started when a patient is intubated and the risk of decompensation due to high dose steroids is minimal. Similarly, acetylcholinesterase inhibitors like pyridostigmine bromide (60–120 mg every 4–6 h) can be started as long as there is no worry about secretions leading to respiratory compromise. Long-term, steroid-sparing agents (see below) will need to be added based on the response to steroids and the ability to taper them.

In patients with milder disease, pyridostigmine is initiated at 30–60 mg every 6 h and then increased to 60–120 mg every 4–6 h. However, patients can develop cholinergic side effects, and even cholinergic crisis if doses become excessive. Except for some patients with ocular MG, patients are rarely controlled with pyridostigmine alone, requiring the addition of immunomodulating medication to control the disease. Prednisone is the mainstay of treatment. While a high dose prednisone regimen may allow for faster improvement, it can also paradoxically worsen MG, especially in the first week of treatment. Because of this, there are two treatment approaches—a “high dose approach” where patients are started at

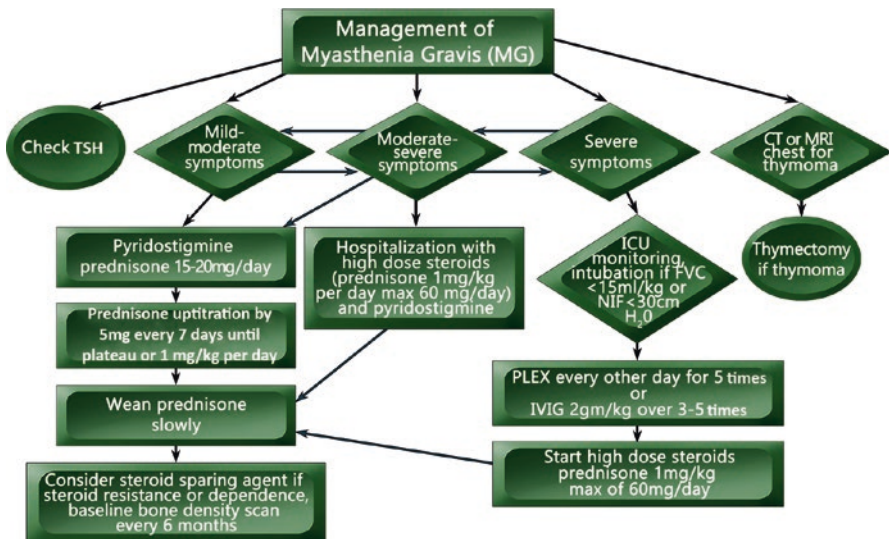


Fig. 15.3 Management of myasthenia gravis (MG)

1–1.5 mg/kg/day of prednisone and slowly tapered down (with hospitalization during the first week to monitor for worsening), or more commonly a “start low and go slow approach,” which starts at 15–20 mg per day and then increases by 5 mg every 7 days until a beneficial effect is seen or the patient reaches 1–1.5 mg/kg (maximum 100 mg) daily. Once strength has stabilized for a few weeks, prednisone is slowly weaned to the lowest possible dose, to prevent steroid side effects. In order to minimize side effects for patients who do not respond to maximal doses of prednisone or cannot be weaned off prednisone, steroid-sparing agents can be used. Common medications include azathioprine, cyclosporine, mycophenolate, tacrolimus, methotrexate, cyclophosphamide and rituximab. Choice of steroid-sparing agent depends on the medical comorbidities of the patient.

All patients with thymoma should undergo thymectomy. Recently, a randomized trial suggested that thymectomy in AChR antibody positive patients aged 18–60, without thymoma, may provide a therapeutic benefit [10]. Currently, thymectomy can be considered as an option to increase the probability of improvement or remission of MG; however, its benefits would need to be weighed with surgical risk in elderly patients.

Lambert-Eaton Myasthenic Syndrome

In contrast to the bimodal distribution of MG, patients with Lambert-Eaton Myasthenic Syndrome (LEMS) are often older, with 84% of patients presenting after age 40, with a mean age of 54 [1].

Clinical Manifestations

Patients with LEMS similarly complain of weakness and easy fatigability, though oftentimes the degree of functional impairment may be out of proportion to the degree of weakness found on examination. Generally, patients complain of difficulty walking. Proximal lower extremity muscles are most affected, although the upper extremity proximal muscles are often also involved. Bulbar and ocular muscles are affected, but less often and less severely than in MG. Some patients may complain of muscle aches or stiffness. Dry mouth and eyes can be found, along with other autonomic symptoms such as blurred vision, constipation, impotence and decreased sweating. Strength may improve temporarily after short exercise.

Examination is similar to the examination for MG, with the caveat that short exercise *improves* muscle strength. Thus, proximal hip and shoulder muscles often begin weak, become stronger with repetitive testing, and then decline in strength after several minutes. Similarly, reflexes may initially be diminished or absent, but are amplified after muscle contraction. Autonomic signs may also be seen, such as sluggish pupillary constriction to light, decreased sweating, or postural hypotension.

In the elderly, LEMS is a paraneoplastic disorder in 1/2 to 2/3 of patients [1]. The majority of patients have small cell lung cancer (SCLC), although lymphoproliferative disorders, pancreatic, breast and ovarian carcinomas have been associated with LEMS as well. Thus, a detailed smoking history and cancer screening history should be obtained in all patients. Patients with LEMS associated with anti-Hu antibodies may also develop cerebellar ataxia, limbic encephalitis or sensory neuronopathy. In other, and predominantly younger, patients LEMS can be due to an autoimmune process and may be accompanied by other disorders such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, and even MG [1, 3].

Diagnostic Approach

Laboratory

Testing for LEMS includes electrodiagnostic and serologic testing (Fig. 15.2). 85–90% of patients will have P/Q type voltage gated calcium channel antibodies. Some patients with paraneoplastic LEMS may also have anti-Hu antibodies, with associated syndromes noted above. AChR binding antibodies may be seen in LEMS patients, and may be non-pathogenic, or be associated with symptoms of MG as well [1].

Electrophysiology

On nerve conduction testing in EMG, motor amplitudes are usually reduced, and usually improve after brief exercise testing or high frequency stimulation, confirming a pre-synaptic NMJ disorder.

Imaging

Patients that are diagnosed with LEMS should be screened for underlying malignancy. Given the strong association with SCLC, CT or MRI of the chest should be performed, and bronchoscopy considered in patients who are smokers with normal imaging. The search for malignancy should be repeated based on the age, risk factors, and symptoms of the patient. If malignancy is found, the tumor should be removed if possible, with appropriate adjuvant therapy [3].

Therapy

Pyridostigmine can be used to treat patients with LEMS, though the response usually is minimal. Amifampridine (3,4 diaminopyridine) has been approved in Europe for LEMS. Amifampridine is currently undergoing trials in the U.S, and can be prescribed on a compassionate use basis. IVIG and plasmapheresis are effective

treatments for symptoms, but are not long lasting. The immunosuppressive medications that are used in MG can be considered for LEMS, although there is concern for tumorigenicity, and the response may be minimal [1, 3].

Of note, there are other rare NMJ disorders, such as botulism, tick paralysis, medication and toxin-induced NMJ disorders, and congenital myasthenic syndromes, which may rarely be found in elderly patients, whose discussion is beyond the scope of this chapter.

Myopathies

In comparison to the fluctuating course of neuromuscular junction disorders, myopathies generally present with *slowly progressive, fixed weakness and muscle wasting*. Myopathies can be due to inflammatory, infectious, endocrine, metabolic, toxic, hereditary, or other causes. When approaching myopathies, six questions can provide a framework to help determine the type of myopathies as suggested by Jackson and Barohn: (1) Which “positive” and/or “negative” symptoms does the patient experience? (2) What is the temporal evolution? (3) Does the patient have a family history of a myopathy? (4) Are there precipitating factors that trigger episodic weakness or stiffness? (5) Are there any associated systemic symptoms or signs present and (6) What is the distribution of weakness? Answers to these questions often help define diagnostic workup [4]. For the purpose of this chapter, we will focus on the most common subgroup of myopathies in the elderly, the inflammatory myopathies, with special attention to inclusion body myositis, and immune-mediated necrotizing myopathy, and a few words about dermatomyositis and polymyositis.

Inclusion Body Myositis

Inclusion body myositis (IBM, or sporadic inclusion body myositis) is the most common cause of inflammatory myopathy in patients over 50 years of age. It is more common in men than women, and is more common in Caucasians.

Clinical Manifestations

IBM presents with slowly progressive, usually *asymmetric weakness, with early involvement and atrophy of the quadriceps, wrist and finger flexors and the ankle dorsiflexors* (Fig. 15.4). Because of this pattern of weakness, patients often complain of difficulties with ambulation and weakened grip strength. IBM can also be associated with dysphagia, facial weakness, and neck flexor weakness as well. On physical examination, the finger and wrist flexors (especially the flexor digitorum profundus, that flexes the last phalanx of the fingers), and to a lesser extent the elbow flexors and extensors, are weaker than the shoulder abductors. In the lower



Fig. 15.4 Photographs—Inclusion body myositis. (a) Knee extensor weakness—note the inability to extend knees to neutral position. (b) Flexor digitorum profundus weakness—note the inability to flex the distal phalanx of the fingers, with sparing of the more proximal flexor digitorum superficialis. (c)—Note atrophy of the medial forearm (finger and wrist flexor muscles)

extremities, the knee extensors and ankle dorsiflexors are the same or usually weaker than the hip flexors. This pattern is highly specific and differentiates IBM from many other myopathies, which present with the typical “limb-girdle” distribution. While this pattern of asymmetric weakness may be mistaken with amyotrophic lateral sclerosis (ALS) clinically, the hand intrinsic muscles are often spared in IBM, contrary to what is seen in ALS. In addition, in IBM, reflexes are normal to slightly reduced, with patellar reflexes being lost early, and there are no upper motor neuron findings. Although patients usually do not have sensory symptoms, a mild sensory peripheral neuropathy can sometimes be found on examination [1, 5].

Diagnostic Approach

Laboratory

On laboratory evaluation, serum creatinine kinase (CK) is normal or only mildly elevated (usually <tenfold above normal).

Electrophysiology

EMG generally demonstrates abnormal spontaneous activity and myopathic units.

Imaging

Magnetic Resonance Imaging (MRI) of affected skeletal muscles can demonstrate atrophy and increased T2 signal.

Other Ancillary Tests

Muscle biopsy demonstrates endomysial inflammation with inflammatory cells surrounding and invading nonnecrotic muscle fibers, myofiber necrosis, regeneration, variation in fiber size and groups of small fibers. The hallmark findings in IBM are the presence of rimmed vacuoles and tubulofilaments on electron microscopy, although these may be absent in 20–30% of biopsies in patients with IBM. Other muscle biopsy findings may include the presence of cytochrome c oxidase (COX) negative fibers and succinic dehydrogenase (SDH) positive muscle fibers, expression of major histocompatibility complex class I on myofibers, and congophilic inclusions in vacuolated fibers. In order to clarify the diagnosis of IBM, the European Neuromuscular Center proposed research criteria in 2011, classifying patients into having clinico-pathologically defined IBM, clinically defined IBM and probable IBM based on clinical and laboratory features and muscle biopsy results [6].

More recently, an antibody that is highly specific for IBM has been discovered. This antibody against cytosolic 5'-nucleotidase 1A (anti-5NTC1A) has been detected in up to 2/3 of patients with IBM, which may provide more diagnostic criteria in the future. Similarly, aggregates of p62 and of transactive response DNA-binding 43 (TDP-43) in cytosolic inclusions in muscle biopsies have also been proposed to have diagnostic utility for IBM as well [7].

Therapy

IBM is notoriously unresponsive to immunomodulatory treatment, and for many years, treatment was supportive, with physical therapy, bracing and assistive devices. However, the search for treatment options is ongoing. Bimagrumab, a monoclonal antibody that binds activin type II receptors, was recently used in a small placebo controlled trial, and demonstrated increased thigh muscle mass on MRI and possible improved 6 min walking distance (6MWD) [8]. A large-scale international double-blind placebo-controlled trial; however, failed to reach the primary endpoint of improving 6MWD or improvement in muscle strength (presented as meeting abstract). Small scale studies on follistatin gene therapy (a gene that promotes muscle growth), and arimoclomol (a medication that amplifies cytoprotective heat shock gene expression) are also planned [7].

Immune-Mediated Necrotizing Myopathy

Clinical Manifestations

Another type of inflammatory myopathy that can be found in the elderly is immune-mediated necrotizing myopathy (INM). Patients present with *acute to subacute myalgias and proximal weakness, generally sparing bulbar muscles*. Serum CK is usually markedly elevated. The most common type seems to be triggered by statin use or presents as part of a paraneoplastic syndrome.

Diagnostic Approach

Laboratory

Patients over the age of 50 that have statin-associated INM often have antibodies against hydroxymethylglutaryl coenzyme A (anti-HMGCoA) reductase. Patients may have positive anti-nuclear antibodies, suggestive of an underlying connective tissue disorder. Some patients may have a positive test for myositis specific antibodies such as anti-signal recognition particle antibody (anti-SRP) [1, 9].

Electrophysiology

EMG demonstrates abnormal spontaneous activity and myopathic units.

Imaging

MRI may demonstrate T2 signal abnormalities in affected muscles that may be suggestive of inflammation or edema.

Other Ancillary Tests

Diagnosis is made by muscle biopsy, in which the most prominent feature is scattered necrotic muscle fibers. Inflammatory infiltrates are rare and confined mainly to necrotic muscle fibers, and the membranes of non-necrotic fibers usually express major histocompatibility complex (MHC-1) and membrane attack complex. Thickened, pipestem capillaries may also be seen. Patients should be screened for malignancy—the most common associated malignancies include gastrointestinal tract adenocarcinomas and small cell and non-small cell carcinomas of the lung [9].

Therapy

Treatment is similar to treatment of other inflammatory myopathies (see below), though one may need to take a more aggressive approach, as some (such as statin-associated INM) may prove resistant to therapy with a single disease-modifying agent.

Dermatomyositis and Polymyositis

The other inflammatory myopathies, dermatomyositis (DM) and polymyositis (PM), can also present with *progressive weakness, over weeks or months, in proximal greater than distal muscles, particularly in the legs*. They have a female predominance. DM may present in children or adults, and PM in adults. Both are found less commonly in the elderly, in their initial presentation, and thus we will discuss them only briefly.

Dermatomyositis

Clinical Manifestations

The weakness in DM is generally preceded or accompanied by a rash, although less frequently the rash follows the myopathy or does not form at all. The most classic rashes include: (1) heliotrope rash—purplish discoloration of the eyelids associated with periorbital edema, (2) Gottron papules—papular, erythematous rash over the knuckles (Fig. 15.5). Patients with DM also may have dilated capillary loops and thrombi seen in their nailbeds, and an erythematous, macular, photosensitive rash over the face, neck and chest (V-sign), shoulders and upper back (shawl sign) or extensor surfaces of joints (Gottron sign). Subcutaneous calcifications mostly occur in juvenile DM, and only rarely in adults. DM can be associated with cardiac, pulmonary, gastrointestinal, rheumatologic manifestations, and is also associated with malignancy in 6–45% of patients. Thus, comprehensive annual histories and physicals with malignancy screening are advocated in patients with DM.

Diagnostic Approach

Laboratory

CK is often elevated in DM, as is aldolase. Antinuclear antibodies (ANAs) are detected in 24–60% of patients with DM. Myositis specific antibodies (MSA)—antisynthetases (for example, anti-Jo-1), anti-signal recognition particles, and

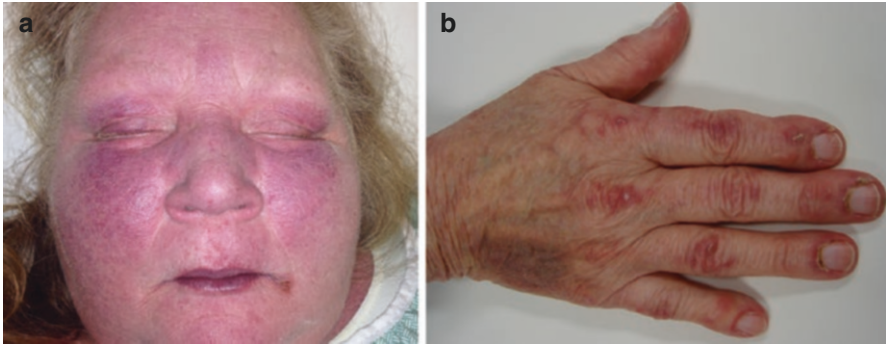


Fig. 15.5 Photographs—Skin changes seen in dermatomyositis. (a)—heliotrope rash—note the purplish discoloration of the eyelids and periorbital edema. (Patient consent for photo (a) obtained by Dr. Salajegheh) (b)—Gottron papules—note the papular, erythematous rash over the knuckles and interphalangeal joints and periungual erythema. (b). (Photo courtesy of Dr. Anthony A. Amato)

anti-Mi2 antibodies may be helpful in predicting response to therapies, but have not been demonstrated to be pathogenic themselves, and their clinical usefulness is still being researched. Anti-Jo-1 is associated with interstitial lung disease [9].

Electrophysiology

EMG shows abnormal spontaneous activity with fibrillation potentials and positive sharp waves, and myopathic units.

Other Ancillary Tests

Diagnosis is made by muscle biopsy, which classically shows perifascicular atrophy. Perivascular inflammatory infiltrates containing macrophages, B cells and CD4⁺ T cells may be found, as well as membrane attack complex deposition around small blood vessels.

Polymyositis

Clinical Manifestations

PM also presents with proximal limb weakness over weeks to months. Approximately 1/3 of patients also complain of swallowing difficulties, although mild facial weakness is only occasionally seen. Similar to DM, PM can be associated with cardiac, pulmonary and joint involvement, and also is associated with a slightly higher incidence of malignancy, though less than DM.

Diagnostic Approach

PM also presents with elevated CK. EMG also shows abnormal spontaneous activity with fibrillation potentials and positive sharp waves, and myopathic units. Diagnosis is again made by muscle biopsy, with mononuclear inflammatory cells surrounding and invading non-necrotic endomysial muscle fibers expressing major histocompatibility complex-1 antigen.

Therapy

In any case, the treatment of DM, PM and INM is dependent on immunosuppression. The standard of care is high-dose steroids—usually prednisone 60 mg/day or, in severe weakness, IV methylprednisolone 1 g/day for 3 days, followed by high dose oral steroids. Once muscle strength and CK normalizes, prednisone can be slowly weaned. Steroid sparing agents can be considered, such as methotrexate, azathioprine, mycophenolate, IVIG, rituximab, cyclosporine, tacrolimus, cyclophosphamide, rituximab and the choice between these agents, similar to the case with MG, depends on the medical comorbidities and the clinical severity of the patient [1, 9].

Other Myopathies

Other myopathies, including hereditary and acquired forms, such as myotonic dystrophy type 1 and 2, limb-girdle muscular dystrophies, metabolic and mitochondrial myopathies, toxic and endocrine myopathies may also be present in elderly patients, whose discussion is beyond the scope of this chapter and could be further explored in other sources noted below.

Conclusion

The differential diagnosis of NMJ disorders and myopathies is broad, similar to the differential diagnosis of weakness described above. The list includes stroke, parkinsonism, gait instability from vascular dementia or other causes, cervical and lumbar spinal stenosis, motor neuron diseases (i.e. amyotrophic lateral sclerosis), acute and subacute demyelinating and axonal neuropathies, and sarcopenia of aging, amongst other diagnosis. However, the clinical history and examination, and ancillary testing, especially electrodiagnostic testing and muscle biopsy in the case of myopathies, are invaluable in diagnosing these NMJ disorders and myopathies.

ICD-10 Codes

Myasthenia gravis without acute exacerbation G70.00

Myasthenia gravis with acute exacerbation G70.01

Lambert-Eaton Syndrome, unspecified (not associated with neoplasm) G70.80

Lambert-Eaton Syndrome in disease classified elsewhere (not associated with neoplasm) G70.81

Lambert-Eaton Syndrome in neoplastic disease G73.1

Inclusion body myositis G72.41

Other inflammatory and immune myopathies, not elsewhere classified G72.49 (for immune-mediated necrotizing myopathy)

Polymyositis with organ involvement unspecified M33.20

Polymyositis with respiratory involvement M33.21

Polymyositis with myopathy M33.22

Polymyositis with other organ involvement M33.29

Dermatopolymyositis with organ involvement unspecified M33.90

Dermatopolymyositis with respiratory involvement M33.91

Dermatopolymyositis with myopathy M33.92

Dermatopolymyositis with other organ involvement M33.99

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Chapter 16

Peripheral Neuropathy and Amyotrophic Lateral Sclerosis

Nimish J. Thakore and Erik P. Pioro

Abbreviations

ALS	Amyotrophic lateral sclerosis
CIAP	Chronic idiopathic axonal polyneuropathy
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CMT	Charcot-Marie-Tooth syndrome
DSP	Distal symmetric polyneuropathy
EDX	Electrodiagnostic testing
FAP	Familial amyloid polyneuropathy
FVC	Forced vital capacity
GBS	Guillain-Barré syndrome
GTT	Glucose tolerance test
HNPP	Hereditary neuropathy with liability to pressure palsies
IGT	Impaired glucose tolerance
LMN	Lower motor neuron
MAG	Myelin-associated glycoprotein
MGUS	Monoclonal gammopathy of undetermined significance
MMN	Multifocal motor neuropathy
NIPPV	Non-invasive positive pressure ventilation
PEG	Percutaneous endoscopic gastrostomy
RLS	Restless legs syndrome
SNRI	Serotonin norepinephrine reuptake inhibitor
TCA	Tricyclic antidepressant
TTR	Transthyretin
UMN	Upper motor neuron

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Clinical Pearls

- Causes, severity, and patterns of progression are diverse in peripheral neuropathies.
- Atypical neuropathies, although uncommon, require prompt recognition and referral to a neuromuscular specialist for further investigation and potentially treatment.
- A mild chronic neuropathy that follows a distal symmetric pattern, and has an evident etiology (such as diabetes, alcohol, or previous neurotoxic chemotherapy exposure) may not require specialty consultation nor electrodiagnostic testing.
- The diagnosis of ALS has profound socioeconomic and psychological implications for patients and their families. It is best approached by a neurologist with experience in the diagnosis and management of ALS. Ongoing care of patients with ALS by a multidisciplinary team may improve quality of life and survival.

Introduction

This chapter covers two groups of disorders that share a common anatomical substrate (the peripheral nervous system), but are strikingly different in their biology, prevalence, clinical presentations, and prognosis. Polyneuropathy is common, affects up to 8% of the population older than 50 years [1], is diverse in its cause (often symptomatic of a underlying systemic disorder such as diabetes), often presents with sensory symptoms or pain, and usually has a chronic benign course. Amyotrophic lateral sclerosis, on the other hand, is an uncommon although not rare (lifetime risk about 1/400) [2] relatively homogenous primary neurodegeneration that largely manifests with muscle weakness/atrophy, and is fatal (median survival is about 3 years).

Peripheral Neuropathy [3]

The terms polyneuropathy, peripheral neuropathy, and (unqualified) neuropathy are used interchangeably and loosely herein and elsewhere to imply a generalized disorder of peripheral nerves, usually involving sensory as well as motor fibers, and usually in a more distal distribution. The most restrictive meaning of polyneuropathy is a symmetrical distal (or length-dependent) disorder involving the peripheral nerves. This pattern, also termed *distal symmetric polyneuropathy* (DSP) is the most common phenotype of neuropathy seen in practice [4, 5]. It manifests with distal sensory symptoms/signs with or without pain starting in the toes and feet bilaterally. It is often associated with distal muscle atrophy and mild weakness (in feet and toes), and ankle hypo-/areflexia. With progression, sensory symptoms/signs ascend symmetrically up the feet and lower legs in a graded stocking distribution, and in

sufficiently severe cases, involve the fingers and anterior abdomen when leg symptoms have ascended to at least the knees. Deviations from this DSP pattern (atypical cases) carry diagnostic implications for cause [6].

Causes and Types of Polyneuropathy

Increasing age is a risk factor for polyneuropathy [7]. Worldwide, the leading cause of polyneuropathy is diabetes, accounting for 30–50% of cases. Other prevalent causes are alcoholism, nutritional deficiency, toxic neuropathy, HIV infection, paraproteinemia-associated neuropathy and hereditary neuropathies. In certain geographical areas, leprosy, familial amyloid polyneuropathy and nutritional neuropathies are common. A large minority of cases (25–40%) in which no cause of polyneuropathy is found is termed cryptogenic polyneuropathy, idiopathic polyneuropathy, or chronic idiopathic axonal polyneuropathy (CIAP). CIAP has a DSP pattern, a very indolent course, and a generally favorable prognosis for gait and motor function over decades.

The prevalence of type 2 diabetes is rising and is 8–9% of the adult population worldwide at the time of this writing [8]. About half of diabetics eventually develop symptoms or signs of polyneuropathy over decades of follow-up [9]. The additional 10–15% of the population who have impaired glucose tolerance (IGT) or “pre-diabetes” may also be at higher risk of developing polyneuropathy, although this is controversial [10]. Type 1 diabetes, although less prevalent, is likewise associated with polyneuropathy. Mechanisms by which hyperglycemia induces nerve damage are complex, numerous (metabolic, vascular, inflammatory) and incompletely understood. Better glycemic control is associated with a lower incidence of neuropathy and slower progression. Diabetic neuropathy tends to follow the DSP pattern, and is usually axonal in nature, although modest motor conduction velocity slowing in some cases may lead to diagnostic confusion with CIDP (chronic inflammatory demyelinating polyradiculoneuropathy, see below). Diabetic neuropathy may be painful or conversely, asymptomatic. Because insensate feet are at risk of foot infection or injury (Charcot’s arthropathy), screening for asymptomatic neuropathy with a 10 g monofilament or tuning fork is recommended in diabetics. Course tends to be chronic and indolent, although acute and self-limited forms are described with abrupt changes in glycemic control (*treatment-related acute painful neuropathy*, or *insulin neuritis*), without or with weight loss (*diabetic neuropathic cachexia*) [11]. Severe weakness (such as foot drop) may result from advanced neuropathy in poorly controlled diabetics, although such motor involvement should warrant careful exclusion of other causes. An asymmetrical proximal form involving lumbar roots/plexus (*diabetic amyotrophy*, or *radiculoplexus neuropathy*) presents acutely over weeks, with pain and marked weakness of one of the thighs and associated constitutional symptoms. After reaching a nadir lasting several weeks to a few months, there is spontaneous but incomplete recovery. Vascular and inflammatory mechanisms may participate in this process. Similar involvement of thoracic roots (*diabetic truncal neuropathy*) and even cervical roots may occur. *Autonomic neuropathy* is common in diabetes,

manifesting with impotence, orthostatic hypotension, gastroparesis and other gastrointestinal dysmotility, distal anhidrosis and gustatory sweating. Autonomic cardiovascular dysfunction is associated with higher mortality.

Alcoholic polyneuropathy has a chronic DSP pattern that is generally relatively mild, caused by a combination of nutritional (especially thiamine deficiency) and direct toxic effects. Other *toxic neuropathies*, such as from medications (see Table 16.1), heavy metals (arsenic, mercury, lead, thallium), or industrial toxins (such as n-hexane, acrylamide, ethylene glycol, organophosphates) can have a variable phenotype [12]. Most tend to be relatively acute or subacute in onset, axonal and of variable severity. Some may be associated with severe motor weakness (heavy metals), while others (notably from platinum-containing agents and pyridoxine) are pure sensory neuropathies. Neuropathy from amiodarone, chloroquine and other amphiphilic agents has mixed axonal and demyelinating features, and may be overshadowed by a toxic vacuolar myopathy. Neuropathy is a consistent and dose-limiting adverse effect of chemotherapeutic agents. *Coasting*, or progression of neuropathy symptoms for months despite discontinuation of the offending agent, is common.

Deficiency of vitamin B12, thiamine (vitamin B1), niacin, multiple B complex vitamins, copper or vitamin E causes polyneuropathy [13]. Nutritional deficiencies may result from dietary habits (vegans), eating disorders, socioeconomic and cultural factors, gastric bypass surgery, bowel resection, celiac disease or other cause of malabsorption. In general, nutritional neuropathies have a chronic or subacute DSP pattern; Vitamin B12 and copper deficiency may cause additional spinal cord involvement (*myeloneuropathy*), which can manifest with early sensory symptoms in the hands, hyperreflexia and ataxia.

Systemic disorders, especially autoimmune conditions such as medium and small vessel vasculitides, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, Sjögren syndrome, scleroderma, celiac disease and inflammatory bowel disease are associated with polyneuropathy. Prevalence and patterns of neuropathy vary. Vasculitis from polyarteritis nodosa, Churg-Strauss syndrome, granulomatous polyangiitis, and cryoglobulinemia frequently causes nerve ischemia and a multifocal or asymmetrical neuropathy that may be acute/subacute, painful, and severe with marked weakness (*mononeuritis multiplex*). A similar pattern may be seen with chronic severe rheumatoid arthritis, although more commonly a mild DSP or entrapment is seen. Sjögren syndrome has a specific association with a pure sensory ataxic neuronopathy that can be severe. Sarcoidosis may cause mononeuritis multiplex as well as exclusive involvement of small fibers. Celiac disease, inflammatory bowel disease and other autoimmune disorders have a weak association with a chronic DSP. The majority of patients with advanced chronic kidney disease (uremia) have a DSP that is mild and often asymptomatic. Hypothyroidism is weakly associated with a mild DSP. Protracted critical illness is associated with a severe axonal sensorimotor neuropathy, with or without a severe myopathy (*critical illness polyneuropathy* and myopathy respectively). *Paraneoplastic neuropathy* is rare and usually manifests as a subacute ataxic sensory or sensorimotor neuronopathy that is non-length-dependent, asymmetric and severe.

Diverse infections have been linked to neuropathy. HIV, especially with low CD4 counts, can cause a DSP that is painful. Cytomegalovirus infection causes a severe

Table 16.1 Commonly used medications that can cause polyneuropathy

Medication class	Comments
<i>Chemotherapeutic agents</i>	Leading cause of toxic neuropathies; often dose limiting; “coasting” is common
Vinca alkaloids (vincristine, vincastine)	Axonal sensory or sensorimotor DSP pattern; affects axonal transport by interfering with microtubule assembly
Taxanes (docetaxel, paclitaxel)	Axonal sensory or sensorimotor DSP pattern; affects axonal transport by interfering with microtubule function
Platinum derivatives (cisplatin, carboplatin, oxaliplatin)	Sensory neuronopathy; permanent damage to dorsal root ganglia
Bortezomib (myeloma)	Axonal sensory or sensorimotor DSP pattern
Thalidomide (myeloma)	Axonal sensory or sensorimotor DSP pattern Novel chemotherapy-associated neuropathy
Immune checkpoint inhibitors (nivolumab, ipilimumab)	Immune-mediated neuropathies resembling Guillain-Barre syndrome or CIDP
<i>Antimicrobials</i>	
Dapsone	Length-dependent motor-predominant neuropathy
Metronidazole	Axonal sensory or sensorimotor DSP pattern
Isoniazid	Axonal sensory or sensorimotor DSP pattern. Can be prevented by supplementing pyridoxine
Nitrofurantoin	Axonal sensory or sensorimotor DSP pattern. Impaired renal function is a risk factor
Nucleoside analogue reverse transcriptase inhibitors (zalcitabine, didanosine, stavudine)	Distal sensory neuropathy, painful, acute/subacute. Differentiated from HIV-associated distal sensory polyneuropathy by acuity of onset, elevated lactate and improvement with discontinuation
Linezolid	Sensory neuronopathy with chronic use
Fluoroquinolones	Equivocal evidence of causation of small fiber sensory neuropathy
<i>Rheumatological agents</i>	
Colchicine	Myoneuropathy; axonal sensory or sensorimotor DSP pattern; renal failure is a risk factor
Hydroxychloroquine, Chloroquine	Myoneuropathy; mixed axonal and demyelinating sensorimotor; renal failure is a risk factor
Gold	Demyelinating sensorimotor neuropathy; myokymia
<i>Cardiovascular agents</i>	
Amiodarone	Myoneuropathy; mixed axonal and demyelinating sensorimotor; tremor; cumulative dose-dependent
Procainamide, perhexiline	Demyelinating sensorimotor polyneuropathy
Hydralazine	Rare. Axonal sensory or sensorimotor DSP pattern. Secondary to pyridoxine deficiency
<i>Other</i>	
Phenytoin	From prolonged use. Often asymptomatic
Pyridoxine	Sensory neuronopathy

polyradiculoneuropathy. Acute HIV infection may be associated with Guillain-Barré syndrome. In many tropical countries, leprosy (a chronic mycobacterial infection) causes either a multifocal neuropathy (with thickened nerves and insensate hypopigmented skin patches), or a diffuse cutaneous neuropathy. Lyme disease can cause a polyradiculoneuropathy. West Nile virus and some enteroviruses can cause an acute motor neuronopathy (acute flaccid paralysis) that resembles poliomyelitis and may be confused with Guillain-Barré syndrome (GBS). Guillain-Barre syndrome has recently been reported with Zika virus infection. In addition, several antiretroviral agents cause a polyneuropathy (Table 16.1).

About 10% of patients with otherwise unexplained neuropathy have a paraproteinemia, usually *monoclonal gammopathy of undetermined significance (MGUS)* [14]. MGUS prevalence increases with age, occurs in 5% of individuals older than 70, and carries a 1% annual risk of progression to malignancy (usually myeloma). About one in six patients with MGUS have IgM MGUS, which subtype largely drives the association with neuropathy. Half of all MGUS-associated polyneuropathy have IgM-MGUS, and contrarily, more than a third of IgM-MGUS develop polyneuropathy. This polyneuropathy is usually demyelinating in nature, with distal sensory symptoms, diffuse motor conduction velocity slowing and disproportionate prolongation of distal motor latencies. Half of these IgM-MGUS-neuropathy patients have a specific antibody directed against *myelin-associated glycoprotein (MAG)*, which is causative, and is found deposited in widened Schwann cell lamellae on nerve biopsy. The association of demyelinating or axonal neuropathy with IgA and IgG paraproteinemia is weaker. Other specific neuropathies seen in this setting include: (1) A severe mixed demyelinating and axonal polyneuropathy associated with the syndrome of *POEMS* (polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes), seen with IgG or IgA lambda monoclonal protein. Usually, an osteosclerotic myeloma is the cause. In addition to systemic changes, a markedly elevated vascular endothelial growth factor (VEGF) level is seen with *POEMS*. (2) *Acquired primary amyloidosis* from MGUS or isolated light chain disease presenting with a distal neuropathy, autonomic involvement, carpal tunnel syndrome, and systemic symptoms including macroglossia, skin changes (purpura), cardiomyopathy and nephrotic syndrome with renal failure. The diagnosis of amyloidosis may require biopsy of nerve or other tissue (abdominal fat pad, cardiac). (3) Chemotherapeutic agents used for myeloma (thalidomide and bortezomib) resulting in polyneuropathy. Table 16.2 provides guidance for historical and examination findings useful in diagnosing polyneuropathy.

Heredofamilial neuropathies explain up to 10% of otherwise unexplained neuropathy. *Charcot-Marie-Tooth syndrome (CMT)* is the prototypical hereditary neuropathy that has demyelinating (CMT1) and less common axonal (CMT2) forms, each with specific genetically determined types [15]. The commonest, caused by duplication of the PMP22 gene (CMT1A), is autosomal dominant and accounts for about 2/3 cases of CMT1. Other common types are mutations of MPZ (CMT1B), GJB1 (CMTX1, X-linked), and MFN2 (CMT2A). CMT is usually painless and very chronic, and manifests with more motor than sensory symptoms. The clinical hallmarks are foot deformity (high arches and hammer toes), foot drop, and tapered “champagne bottle” legs. CMT may be asymptomatic and occasionally present in

Table 16.2 History and examination findings helpful for diagnosis of polyneuropathy

Finding	Diagnosis
Family history	Charcot-Marie-Tooth syndrome, Amyloid
Alcohol	Alcoholic and nutritional polyneuropathy
Diet (e.g. vegan, no greens, exclusive corn, poverty)	Nutritional: Vitamin B12, thiamine, niacin
Chemotherapy	Toxic neuropathy
Other medications	
Recreational exposure (glue-sniffing, whippets = nitrous oxide)	
Occupational exposure	
Geography/extraction	
HIV/blood borne risk factors	HIV, Hepatitis C-associated, HTLV-1
Constitutional symptoms	Nutritional, inflammatory disorders, vasculitis, HIV, POEMS
<i>Gastrointestinal history or signs</i>	
– Gastric bypass, bowel resection	Nutritional (especially vitamin B12)
– Cirrhosis	Alcohol, hepatitis C, toxins
– Celiac disease	Celiac disease associated, nutritional
– Malabsorption; vomiting	Nutritional
– Inflammatory bowel disease	Inflammatory bowel disease-associated
– Ascites	POEMS, cirrhosis, malignancy
– Organomegaly	POEMS, amyloidosis
– Abdominal pain	Heavy metal toxicity
– Gastroparesis, dysmotility	Autonomic neuropathy
<i>Skin and related</i>	
– Clubbing	POEMS
– Sclerodactyly	POEMS, scleroderma
– Raynauds	Cryoglobulinemia, scleroderma
– Hypertrichosis	POEMS
– Hyperkerotosis, nail changes	Arsenic
– Pigmented dermatitis neck, hands	Pellagra (niacin deficiency)
– Hypopigmented insensate macules	Leprosy
– Purpura	Amyloidosis
– Alopecia	Thallium
<i>HEENT</i>	
– Sicca	Sjögren syndrome
– Papilledema	POEMS, GBS
– Macroglossia	Amyloidosis
<i>Other systems</i>	
– Cardiac	Amyloidosis, diabetes
– Renal	Diabetes, amyloidosis, light chain disease, vasculitis

(continued)

Table 16.2 (continued)

Finding	Diagnosis
– Eosinophilia	Churg-Strauss syndrome
– Thrombocytopenia	Alcohol, HIV, vitamin B12 deficiency
– Hilar and other lymphadenopathy	Sarcoidosis, lymphoma
<i>Extremity change</i>	
– Pes cavus, hammer toes	Marked chronicity, often CMT
– Charcot's foot	Non-specific, in advanced diabetic neuropathy
– Thickened nerves	Demyelinating CMT, CIDP, Leprosy
– Edema	POEMS, amyloid, diabetes, other
– Arthritis	Rheumatoid arthritis
<i>Autonomic symptoms</i>	
– Orthostasis	Autonomic neuropathies
– Impotence	
– Gastrointestinal dysmotility, gastroparesis	
– Distal anhidrosis, gustatory sweating	
– Sicca	
– Bladder dysfunction	

late life. *Hereditary neuropathy with liability to pressure palsies (HNPP)*, an autosomal dominant disorder usually caused by deletion of a PMP22 allele, is clinically and electrophysiologically distinct from CMT1A, presenting with compression/entrapment neuropathies superimposed upon a milder diffuse neuropathy. *Familial amyloid polyneuropathy (FAP)* is an autosomal dominant, adult-onset, progressive and potentially fatal axonal polyneuropathy caused by mutations of the transthyretin (TTR) gene. FAP is prevalent in certain parts of the world (Portugal, Brazil, Japan and Sweden), but is rare in the US. Additional manifestations of FAP may include carpal tunnel syndrome, autonomic neuropathy, cardiomyopathy, gastrointestinal dysfunction, renal failure and oculoleptomeningeal involvement. *Fabry's disease* is an X-linked lysosomal storage disorder caused by α -galactosidase A deficiency that manifests with a small fiber painful neuropathy, groin skin tags, thrombotic complications and renal failure. Fabry's disease may develop in women who are manifest carriers of the abnormal X chromosome. Effective treatments are available for FAP and Fabry's disease. Other hereditary causes include porphyrias (acute severe motor neuropathy resembling GBS, abdominal pain, psychosis), adult polyglucosar body disease (dementia, white matter changes in the brain, and neurogenic bladder), and neuropathy as a part of a neurodegenerative or metabolic disorder (such as Refsum disease, adrenomyeloneuropathy, or spinocerebellar ataxia).

Specific immune-mediated or inflammatory neuropathies are demyelinating and often display involvement of proximal nerve segments, or nerve roots in addition to distal involvement. *Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)*, or *Guillain-Barré syndrome (GBS)* [16], is an acute predominantly motor neuropathy that progresses rapidly over 1–2 weeks, either in an ascending or a descending fashion, often involves cranial nerves (especially causing facial diplegia), may involve respiratory muscles, and result in quadriplegia. GBS is usually not confused with other conditions described previously. *Chronic inflammatory demyelinat-*

ing polyradiculoneuropathy (CIDP) [17] is usually a motor-predominant neuropathy that has acute relapsing and subacute/chronic patterns of evolution. Although CIDP can cause severe proximal and distal weakness, respiratory and cranial muscles are usually spared. The diagnosis of CIDP relies heavily upon electrodiagnostic demonstration of acquired demyelination including segmental slowing, conduction block, and dispersion of motor responses. Weakness of proximal muscles, knee areflexia and elevated CSF protein are supportive. The existence of at least 16 published sets of diagnostic criteria with varying sensitivities and specificities attests to diagnostic challenges [18]. Misdiagnosis is rampant [19]. Multiple variants of CIDP are described, including multifocal sensorimotor (Lewis-Sumner syndrome), multifocal pure motor (multifocal motor neuropathy, or MMN, often associated with GM1 antibodies), sensory, and distal predominant (often associated with paraproteinemia) forms. There are highly effective acute and chronic treatments for GBS and CIDP respectively, including intravenous immunoglobulin (IVIg) and plasma exchange for both, and corticosteroids for the latter. Although the prognosis of both disorders is generally favorable with treatment, a significant minority are left with severe motor disability [20].

Small fiber neuropathy [21] is suspected when the patient has cutaneous sensory symptoms, either distal extremity or diffuse, but no reflex change, weakness or ataxia, and negative electrodiagnostic testing. Small fiber neuropathy may be seen with diabetes, IGT, and a wide range of inflammatory disorders (sarcoidosis, celiac disease, inflammatory bowel disease, Sjögren syndrome and other autoimmune disease), or may be idiopathic. Heredofamilial forms include mutations of α -galactosidase A (Fabry's disease), SCN9A (Na1.7 sodium channel, causing erythralgia or erythromelalgia), and TTR (familial amyloid polyneuropathy) genes. Diagnosis may be confirmed by measurement of intraepidermal nerve fiber density on skin biopsy. Small fiber neuropathy may be associated with autonomic neuropathy, which manifests with distal anhidrosis, orthostatic hypotension, impotence, bladder dysfunction, and gastrointestinal dysmotility. Autonomic neuropathy may be confirmed by tests of cardiovascular and sudomotor autonomic function.

Diagnosis and Management of Polyneuropathy (Figs. 16.1 and 16.2)

Neuropathy symptoms and signs, namely bilateral toe, foot and leg sensory symptoms, pain, and perhaps some degree of distal weakness and gait ataxia can result from neuropathy mimics. The commonest mimic is chronic bilateral S1 radiculopathy, usually from lumbosacral spine degeneration. Back symptoms, a neurogenic claudication history, asymmetry, and muscle atrophy/weakness are clinical markers of radiculopathy. Typically, sural sensory responses are preserved on nerve conduction study in radiculopathy. The diagnoses that carry the highest cost, if not recognized, are myelopathies. These may be compressive (cervical spondylosis, thoracic tumor) or non-compressive (multiple sclerosis, vitamin B12 deficiency). Myelopathies are recognized by hyperreflexia (especially at the knees), truncal sensory symptoms, sphincter symptoms, disproportionate ataxia and proprioceptive sensory loss, and confirmed by appropriate imaging and other tests. Some neuropathies (such as with vitamin B12 deficiency) may be associated with myelopathy (myeloneuropathy).

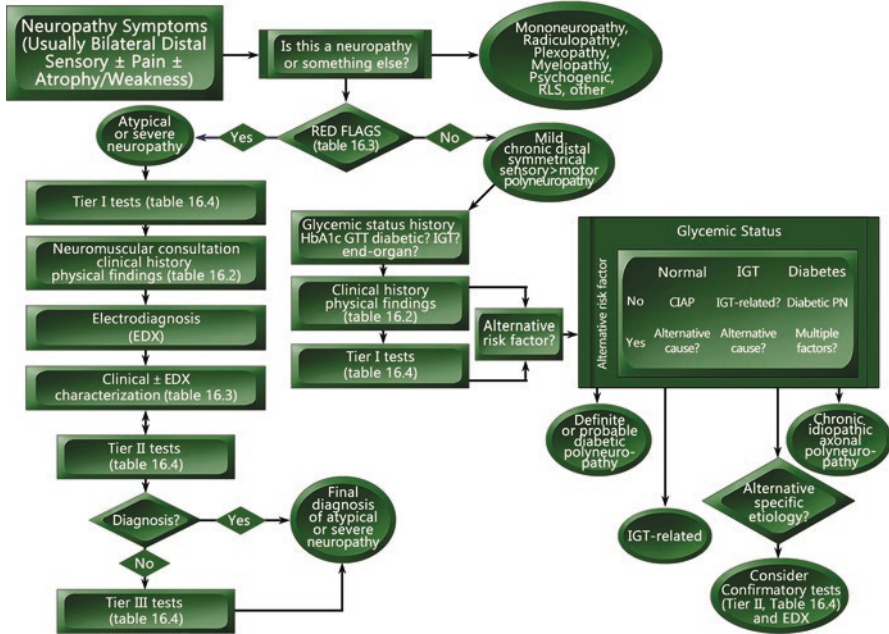


Fig. 16.1 Diagnosis of neuropathy

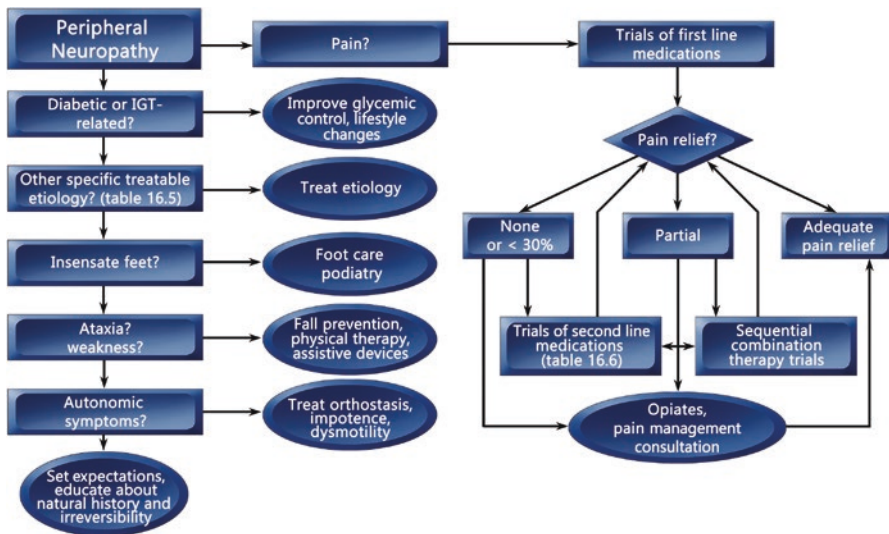


Fig. 16.2 Treatment of neuropathy

Occasionally, mononeuropathies (median—carpal tunnel syndrome, ulnar, radial and peroneal) and plexopathies are confused with general neuropathic processes such as vasculitic neuropathy, Lewis-Sumner syndrome, HNPP, and diabetic amyotrophy.

Restless legs syndrome (RLS) is a prevalent problem that is recognized by specific symptom association with rest and time of day, and relief with activity. RLS symptoms are more proximal than typically seen in polyneuropathy. A polyneuropathy may be associated with RLS. It is critical that the possibility of neuropathy mimics be carefully addressed clinically, and if necessary, by tests (electrodiagnostics, imaging), because several are treatable, and some may have serious long-term consequences if unrecognized. After exclusion of mimics, the accuracy of the positive diagnosis of polyneuropathy depends upon the number of symptoms/signs identified. Overall, physical signs (such as impaired light touch and vibration, ankle areflexia and toe weakness) are more reliable than symptoms (tingling/numbness, pain). Electrodiagnostic testing is most sensitive in detecting large fiber polyneuropathies. Once the diagnosis of neuropathy is established, the next question to ask is if it conforms to a chronic mild DSP, or is an *atypical neuropathy* that raises one of the “red flags” (Table 16.3). These atypical neuropathies can be severe, may

Table 16.3 Red flags for identifying an atypical neuropathy

Feature	Possible diagnostic implication
Acute/Subacute onset and/or Rapid progression	GBS and mimics (porphyria, toxic), CIDP, critical illness neuropathy, toxic, nutritional, vasculitic, paraneoplastic, diabetic amyotrophy, acute painful diabetic neuropathies
Severe sensory loss	Paraneoplastic, Sjögren syndrome, toxic neuropathies (platinum derivatives, pyridoxine), syphilis, idiopathic, IgM-MGUS (including anti-MAG)
Severe ataxia	
Pure sensory neuropathy/neuronopathy	
Severe weakness, motor-predominant	GBS and mimics (porphyria, heavy metal toxicity), CIDP, critical illness neuropathy, multifocal motor neuropathy, POEMS, vasculitic, CMT (distal weakness)
	<i>If pure motor, address possibility of ALS</i>
Non-length-dependent	GBS and mimics, CIDP, critical illness neuropathy, toxic (especially heavy metal), multifocal motor neuropathy, POEMS, diabetic amyotrophy
Quadriceps weakness	
Knee areflexia	
Radiculoneuropathy	
Prominent asymmetry	Vasculitis, multifocal motor neuropathy, CIDP (Lewis-Sumner syndrome), HNPP, superimposed entrapments (CTS in amyloidosis, hypothyroidism, uremia, rheumatoid arthritis)
Mononeuropathies	
Mononeuritis multiplex	
	Address possibility of unrelated radiculopathy; if arm predominant consider neuralgic amyotrophy
Prominent autonomic symptoms or deficits	Diabetes, amyloidosis, paraneoplastic, Guillain-Barré syndrome, porphyria
Primary demyelinating neuropathy	GBS, CIDP, IgM-MGUS (including anti-MAG), CMT1, certain toxic neuropathies (Table 16.1)

be treatable, and almost always require a prompt neuromuscular consultation and careful electrodiagnosis. Chronic mild DSP, on the other hand, may be diabetic, idiopathic, or related to specific etiologies ascertained on history and examination, or on Tier I (Table 16.4) testing. Chronic mild DSP may not need a neurology consultation or electrodiagnostic testing. Tables 16.2 and 16.3 may assist clinicians to suspect the cause of neuropathy. Subsequent testing (Tier II and III, Table 16.4) to confirm should be directed by clinical suspicions. Despite extensive testing, about 25–40% of cases (usually with an indolent DSP) remain undiagnosed. There is wide variation in practice, resulting in considerable cost and waste of resources [23].

It should also be recognized that the vast majority of neuropathies are largely irreversible, especially if there is axon loss. The diagnosis of the cause of polyneuropathy is nevertheless important because neuropathy may be a presenting manifestation of a

Table 16.4 Sequential testing for neuropathy: A representative list and hierarchy of tests for the etiology of polyneuropathy drawn from the authors' personal experience, and supported by evidence and expert opinion [3, 5, 6, 22]

Tests	Comments
TIER I	Recommended for most patients with polyneuropathy
2-h Glucose tolerance test (GTT) or HbA1c	For patients not reporting a history of diabetes. Can diagnose diabetes or impaired glucose tolerance. GTT is more sensitive than HbA1c
Vitamin B12 and/or methylmalonic acid levels	Methylmalonic acid is more sensitive and may be used when vitamin B12 level is low-normal (<300)
Immunofixation electrophoresis	Preferred screening test for paraproteinemia, more sensitive than serum protein electrophoresis
TSH	Commonly done, but low yield and little rationale to support its routine use
Electrodiagnosis	Nerve conduction studies more informative than needle electrode examination. Necessary for diagnosis of demyelinating neuropathy
TIER II	Tailored to clinical suspicion in otherwise unexplained neuropathies
CBC, renal and hepatic function, calcium level, urinalysis	Overall screen for systemic disease
Folate, thiamine, copper, vitamin B6 (pyridoxine), vitamin E levels	For suspected nutritional neuropathies
HIV, Lyme, Syphilis, HTLV-1	
Erythrocyte sedimentation rate and C-reactive protein	Inflammatory disorders
Antinuclear antibody, anti-extractable nuclear antigen (ENA)	Systemic lupus erythematosus, Sjögren syndrome, mixed connective tissue disease
Anti-neutrophil cytoplasmic antibodies (proteinase-3 and myeloperoxidase), cryoglobulin level, hepatitis B and C serology, rheumatoid factor, citrullinated cyclic peptide antibody, complement levels	Vasculitides including granulomatous polyangiitis (Wegener's granulomatosis), Churg-Strauss syndrome, microscopic polyangiitis, rheumatoid arthritis, polyarteritis nodosa, cryoglobulinemic vasculitis, hepatitis infection-associated vasculitis. Also seen with inflammatory bowel disease and liver disease

Table 16.4 (continued)

Tests	Comments
Urine Bence-Jones protein, urine electrophoresis, free light chains	Further testing for paraproteinemic neuropathy, especially if immunofixation electrophoresis is negative and if primary amyloidosis is suspected
Blood and/or urine heavy metals	
Angiotensin converting enzyme	Low sensitivity and specificity test for sarcoidosis.
Vascular endothelial growth factor	Marked elevation quite sensitive and specific for POEMS
Gliadin and tissue transglutaminase antibodies	For celiac disease or gluten sensitivity
TIER III	Requested in specific situations, almost always under the direction of a neuromuscular neurologist
Paraneoplastic autoantibodies	Subacute sensory neuronopathy or sensorimotor neuronopathy. Of little value in DSP
Myelin-associated glycoprotein (MAG), ganglioside (GM1, GQ1b), and other autoantibodies (SGPG, sulfatide, GALOP)	High titers of GM1 are seen in multifocal motor neuropathy; sensitivity is about 50%, but varies depending upon method, at the cost of specificity. GQ1b antibodies are seen in the Miller-Fisher variant of GBS. MAG antibodies should not be tested if there is no IgM monoclonal gammopathy. Other antibodies have uncertain additional value
Genetic testing for Charcot-Marie-Tooth syndrome	Algorithms proceed from common to rare causes, and then invoke next-generation sequencing. They are beyond the scope of this brief review
Transthyretin gene sequencing	Clinical suspicion, family history or biopsy proof of amyloidosis
Skeletal survey	To look for an osteosclerotic myeloma or solitary plasmacytoma that can cause POEMS
Lumbar puncture	Elevated protein in CIDP and GBS. Not specific, may be elevated in diabetes. Pleocytosis in polyradiculopathies
CT chest, abdomen, pelvis	For sarcoidosis (bilateral hilar lymphadenopathy), malignancy, Castleman's disease (may occasionally cause POEMS)
Abdominal fat pad biopsy, other sites	Amyloidosis
Minor salivary gland biopsy, Schirmer test	Sjögren syndrome
Nerve biopsy (usually sural)	Rare indications, overall low to medium sensitivity but high specificity; find another tissue to biopsy, if acceptable. Vasculitis, amyloidosis, sarcoidosis, infiltrations, rare metabolic syndromes (e.g. adult polyglucosan body disease)
Skin biopsy: Intraepidermal nerve fiber density	Most accurate test for pure small fiber sensory neuropathy. Not necessary if electrodiagnostic testing finds large fiber involvement
Autonomic tests: sudomotor, cardiovascular, gastrointestinal motility studies, urodynamics, pupillometry	May be indicated in neuropathies with autonomic dysfunction

serious systemic disorder, such as diabetes, HIV infection or vasculitis. The treatment of polyneuropathy can be divided into two categories: (1) Disease-modifying, directed against the cause of the neuropathy, and (2) Symptomatic and supportive.

Treatment of Neuropathy

Disease-modifying treatment is available only for a minority of neuropathies, as summarized in Table 16.5. Motor deficits of CIDP attributable to demyelination are largely reversible with IVIg or corticosteroids. Incidence and progression of diabetic neuropathy improve significantly with tight glycemic control in Type 1 diabetes [24]. This effect, however, is weak or equivocal in Type 2 diabetes [25]. Uncontrolled diabetes, however, is associated with more rapid progression of neuropathy; therefore it is reasonable to achieve fair glycemic control. For toxic and nutritional neuropathies, elimination of exposure and replenishment, respectively, are appropriate. Immunosuppression can halt or even reverse vasculitic neuropathy. Specific small molecules (tafamidis and diflunisal) effectively treat familial amyloid polyneuropathy and prolong survival [26]. Enzyme replacement is available for Fabry's disease, but effects on neuropathy are modest [27].

Table 16.5 Treatable neuropathies

Diagnosis	Treatment
GBS	Plasma exchange, IVIg
CIDP (including non-IgM kappa MGUS)	IVIg, corticosteroids, plasma exchange, additional chronic immunosuppression
Vasculitic neuropathy	Corticosteroids, cyclophosphamide, steroid-sparing agents, rituximab
IgM MGUS-associated neuropathy (including anti-MAG-associated)	Refractory to corticosteroids, alkylating agents, IVIg. May respond to rituximab
POEMS syndrome	Irradiation of plasmacytoma; for diffuse or refractory disease may need corticosteroids, alkylating agents, lenalidomide, stem cell transplant
Primary systemic amyloidosis (light chain or AL disease)	Corticosteroids, alkylating agents, lenalidomide
Familial amyloid polyneuropathy	Tafamidis, diflunisal, liver transplant
Fabry's disease	Enzyme replacement (α -galactosidase A)
Toxic polyneuropathy	Eliminate exposure; chelating agents for heavy metals
Nutritional neuropathy	Supplement deficiency
Sjögren syndrome associated ataxic sensory neuronopathy	IVIg, plasma exchange, corticosteroids, rituximab, infliximab. Often refractory, no proven treatment
Paraneoplastic neuropathy	May halt with treatment of tumor. Responds poorly to immunosuppression
Infection-related	Treat infection. HIV-related DSP does not usually respond to anti-retroviral treatment

Symptomatic treatment involves pain control, foot care, fall prevention, provision of appropriate assistive devices and treatment of autonomic symptoms (Fig. 16.2). Pain control [28, 29] is initially attempted by the use of a single agent from one of many classes (Table 16.6), starting with a small dose and increasing gradually to the maximum tolerated dose. Choice of medication is determined by comorbidities and age. For instance, antidepressants are favored in depressed patients, while amitriptyline is

Table 16.6 Medications for neuropathic pain

Medication	Daily dose range	Comments
Anti-epileptics		
<i>α-2 δ calcium channel ligands</i>		EFNS (first line)
Pregabalin	75–600 mg	AAN (level A)
Gabapentin	300–3600 mg	AAN (level B)
<i>Sodium channel blockers</i>		AAN (not recommended) EFNS (inefficacy or discrepant results)
Carbamazepine	200–1200 mg	First line for trigeminal neuralgia. Equivocal benefit for neuropathy pain. May help cramps
Oxcarbazepine	300–2400 mg	Equivocal benefit for neuropathy pain. May help cramps
Lamotrigine	50–600 mg	Equivocal benefit for neuropathy pain
Lacosamide	100–400 mg	Equivocal benefit for neuropathy pain
<i>Other</i>		EFNS (inefficacy or discrepant results)
Divalproex sodium	250–1500 mg	AAN (level B)
Topiramate	50–300 mg	Equivocal benefit
Antidepressants		
<i>Tricyclic agent</i>		EFNS (first line)
Amitriptyline	10–150 mg	AAN (level B)
Nortriptyline	10–150 mg	
<i>Serotonin-Norepinephrine reuptake inhibitors (SNRI)</i>		EFNS (first line)
Duloxetine	30–120 mg	AAN (level B)
Venlafaxine	37.5–225 mg	AAN (level B)
Other		
Mexelitine	150–750 mg	AAN (not recommended) EFNS (inefficacy or discrepant results) Similar to sodium channel blocker. Helps cramps
α -Lipoic acid	600 mg	Equivocal symptomatic benefit of oral treatment for neuropathy symptoms
Dextromethorphan	Up to 400 mg 40 mg (with quinidine 20 mg)	EFNS (level B). Available also in combination with quinidine, which increases bioavailability

(continued)

Table 16.6 (continued)

Medication	Daily dose range	Comments
Topicals		
Capsaicin 0.075%	Topical 3–4 times a day	AAN (level B)
Lidocaine 5% patch	Maximum of three patches on for 12 h	Equivocal benefit
Isosorbide dinitrate spray		AAN (level B)
Opiates		
Tramadol	100–400 mg	AAN (level B)
Morphine, oxycodone, methadone		AAN (level B)
Non-pharmacological		
Transcutaneous electrical nerve stimulation		AAN (level B)
Acupuncture		Insufficient evidence

AAN American Academy of Neurology: Evidence based guideline: Treatment of painful diabetic polyneuropathy (2011) [30]

EFNS EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision [31]

avoided in the presence of autonomic dysfunction and in the elderly, because of risk of orthostasis and anticholinergic side effects. If one agent fails, monotherapy with another agent is attempted, and subsequently, combinations of agents with different mechanisms are tried. Overall, medications are only modestly effective, with numbers needed to treat (for 50% relief) ranging from 2 to 10. In refractory cases, tramadol or low dose opiates are an option. Insensate feet are at risk of chronic trauma and Charcot's arthropathy; appropriate footwear, education in foot care, and periodic inspection by a podiatrist are appropriate, especially in diabetics with a significant polyneuropathy. Gait imbalance may be addressed by physical therapy. Patients with foot drop may benefit from ankle-foot orthoses. Orthostatic hypotension is addressed by thigh-high compression stockings, sleeping in a reverse Trendelenberg position, liberal salt intake, and medications including fluudrocortisone, midodrine, pyridostigmine and droxidopa. Impotence is treated with phosphodiesterase type 5 inhibitors. Gastrointestinal, urological and sudomotor symptoms can also be effectively treated. Most important is education about the natural history and setting realistic expectations about treatment.

Amyotrophic Lateral Sclerosis [32, 33]

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease, is a neurodegenerative disorder that primarily affects motor neurons in the anterior horn of spinal cord (lower motor neurons, or LMNs), and in the motor cortex (upper motor neurons, or UMNs). Loss of LMNs causes weakness and muscle atrophy (amyotrophy). Loss of UMNs causes degeneration with resultant scarring of the lateral tracts of spinal cord (lateral sclerosis). UMN and LMN loss may

Table 16.7 Motor symptoms and signs of ALS

	Lower motor neuron	Upper motor neuron
Cranial/Bulbar	Slurred speech (\pm hypernasal)	Spastic speech (slow, labored)
	Dysphagia	Dysphagia
	Tongue atrophy, fasciculations, and weakness	Slow, restricted tongue movement
	Facial weakness \pm fasciculations	Hyperactive jaw reflex
	Palatal weakness	Hyperactive facial reflexes
	Weak cough	Hyperactive gag reflex
	Dysphonia	Restricted palatal movement
Spinal	Extremity muscle weakness and atrophy, usually distal more than proximal Fasciculations	Spasticity
		Slowness of motor activation
		Hyperactive muscle stretch reflexes
		Hoffmann sign
		Extensor plantar response (Babinski sign)
Truncal muscles	Neck extensor weakness (head drop)	
	Trunk weakness	
	Respiratory muscle weakness	

affect extremity/trunk as well as cranial musculature. Corresponding symptoms and signs are summarized in Table 16.7. ALS is the commonest degenerative disorder of motor neurons in adults, with an annual incidence of 2/100,000, and a prevalence of 5–7/100,000. The male to female ratio is 1.5. Peak age of onset is in the late 50s. Death is usually from respiratory failure, unless tracheostomy and ventilatory support are employed. Median tracheostomy-free survival from onset of symptoms is about 3 years. About 10% survive longer than 10 years. ALS is usually sporadic although about 10% cases are familial.

Clinical Manifestations

ALS is limb-onset in about 70%, where the history typically is of painless progressive weakness and atrophy of muscles of one extremity (arm or leg), without associated sensory loss. With time, there is gradual spread of weakness and atrophy to the contralateral side, and to the other ipsilateral extremity. A clinical hallmark is a weak extremity that simultaneously exhibits muscle atrophy (often with fasciculations) and spasticity with hyperreflexia. About 25% have bulbar-onset ALS, manifesting with dysarthria, dysphagia, tongue atrophy, fasciculations, and weakness, facial fasciculations and weakness, perhaps weight loss, and pseudobulbar signs

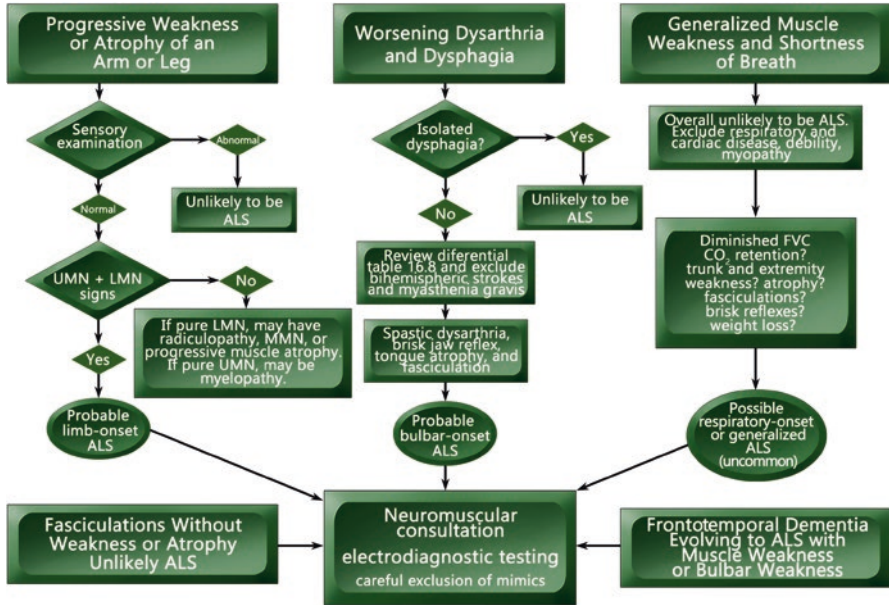


Fig. 16.3 Diagnosis of ALS

including pseudobulbar affect (emotional lability). Bulbar-onset patients are older and more frequently women, and have a poorer prognosis. Occasionally, patients present with generalized weakness or primary respiratory symptoms. Neck extensor weakness, or head drop, may be an early symptom of ALS. The majority of patients with ALS have simultaneous UMN and LMN signs. Some may present with exclusively UMN signs or LMN signs and if they remain as such after at least 3 years from symptom onset, may have primary lateral sclerosis (PLS) or progressive muscular atrophy (PMA), respectively. Although most patients presenting with only UMN or LMN signs eventually progress to develop LMN and UMN features respectively, they tend to have a better prognosis. Diagnosis of such exclusive UMN or LMN presentations requires very careful ruling out of mimics. A significant minority of ALS patients has or develops frontotemporal cognitive deficits, which may reach severity of frontotemporal dementia. Figure 16.3 provides an algorithm for diagnosis of ALS. Table 16.8 provides diagnostic criteria for ALS.

Genetics

The commonest mutations known to cause familial ALS involve C9orf72 (a hexanucleotide repeat expansion that explains up to 50% of cases in some populations), and SOD1 (superoxide dismutase 1 gene, explains up to 20% of hereditary cases).

The diagnosis of ALS carries profound socioeconomic and psychological implications for patients and their families. It almost always requires the involvement of

Table 16.8 Awaji-shima consensus recommendations for the application of electrophysiological tests to the diagnosis of ALS, as applied to the revised El Escorial Criteria

1. Principles
The diagnosis of amyotrophic lateral sclerosis [ALS] requires
(a) <i>the presence of</i>
evidence of <i>lower motor neuron (LMN) degeneration</i> by clinical, electrophysiological, or neuropathological examination
evidence of <i>upper motor neuron (UMN) degeneration</i> by clinical examination; and
<i>progressive spread of symptoms or signs</i> within a region or to other regions, as determined by history, physical examination, or electrophysiological tests
(b) <i>the absence of</i>
<i>electrophysiological or pathological evidence of other disease processes</i> that might explain the signs of LMN and/or UMN degeneration, and
<i>neuroimaging evidence of other disease processes</i> that might explain the observed clinical and electrophysiological signs
2. Diagnostic categories
<i>Clinically definite ALS</i> is defined by <i>clinical or electrophysiological</i> evidence by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions or the presence of LMN and UMN signs in three spinal regions
<i>Clinically probable ALS</i> is defined on <i>clinical or electrophysiological</i> evidence by LMN and UMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs
<i>Clinically possible ALS</i> is defined when <i>clinical or electrophysiological</i> signs of UMN and LMN dysfunction are found in only one region; or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs. Neuroimaging and clinical laboratory studies will have been performed and other diagnoses must have been excluded

a neurologist experienced in the diagnosis and care of ALS. Converging pathways to the diagnosis, for limb onset, bulbar-onset, and diffuse onset cases, are displayed in Fig. 16.3. The differential diagnosis is presented in Table 16.8. Appropriate imaging and laboratory tests are employed to exclude alternative etiologies. Electrodiagnostic testing is critical for confirming LMN involvement, and determining its distribution in the four neuraxial regions (cranial, cervical, thoracic and lumbar). At this time, there is no widely available test for UMN involvement, and determination is entirely clinical. Diagnostic criteria (El Escorial and Awaji-shima) [34, 35] determine level of certainty of diagnosis based upon distribution of LMN and UMN involvement: definite (UMN and LMN each in three or four regions), probable (UMN and LMN each in two regions, with UMN rostral to LMN), and possible (UMN and LMN in one region, or UMN in two regions, or LMN rostral to UMN). Table 16.9 provides the Awaji-shima diagnostic criteria for ALS [35].

Treatment

Between 1995 and 2017, riluzole (in a dose of 50 mg orally twice a day) was the only medication approved for use in the United States to prolong life in ALS. Its effect on survival is quite modest (2–3 months) [36]. Side effects include fatigue,

Table 16.9 Disorders to consider in the differential diagnosis of ALS

Mimic	Diagnostic pointers
<i>UMN and LMN signs</i>	
Cervical spondylotic myelopathy with or without lumbar spondylosis	Commonest differential. Bulbar-sparing, sensory symptoms and pain, chronicity, gait ataxia; MRI cervical spine is diagnostic
Syringomyelia	Dissociated sensory loss arms; MRI Cx spine
Other neurodegenerations	These disorders are rare. They have specific additional clinical findings (such as eye movement abnormality, ataxia, cranial neuropathy or movement disorder), or specific imaging findings. Diagnosis may require genetic testing
– Adult-onset Tay Sach's disease	
– Adult polyglucosan body disease	
– Spinocerebellar ataxias	
– Adult-onset Alexander disease	
<i>UMN signs alone (non-compressive myelopathies)</i>	
Vitamin B12 and copper deficiency	Posterior column sensory loss, ataxia
Multiple sclerosis	History, physical findings, brain MRI
Hereditary spastic paraplegia	Family history, indolent course, worse leg involvement
Adrenomyeloneuropathy	Male gender, adrenal insufficiency, pigmentation, elevated very long chain fatty acids
HIV and HTLV-1 myelopathy	
Stiff person syndrome	Spasms, gait abnormality, elevated GAD antibodies
Parkinson-plus syndromes	Akinetic-rigid syndrome
<i>LMN signs alone</i>	
Cervical or lumbar radiculopathy	Common differential. MRI cervical or lumbar spine
Multifocal motor neuropathy	Distribution of weakness. Block on EMG. GM1 antibodies
Hirayama disease	Segmental hand/arm involvement in youth, MRI cervical spine in flexion and extension
Kennedy's disease	Man with bulbar weakness, tongue fasciculations, gynecomastia, tremor, prominent cramps, loss of sensory responses on EMG, genetic testing (androgen receptor gene)
Spinal muscular atrophy (type IV) and hereditary motor neuropathies	Diverse and rare genetic disorders, generally presenting in youth with a slowly progressive disorder
Post-polio muscular atrophy	History of poliomyelitis
Chronic inflammatory demyelinating polyradiculoneuropathy	Sensory symptoms and signs, areflexia, demyelination on electrodiagnostic testing
Paraproteinemic and other severe polyneuropathies	History, sensory symptoms and signs, appropriate tests
Paraneoplastic motor neuropathy	Atypical subacute presentation, blood tests and CSF
Inclusion body myositis	Predominant quadriceps and finger flexor weakness, chronicity. CK, electrodiagnostic testing, muscle biopsy
Lambert-Eaton myasthenic syndrome	Areflexia, fatigability, bulbar and autonomic changes. Electrodiagnosis and P/Q type calcium channel antibodies
Hyperthyroidism	No UMN nor LMN sign. Weight loss, hyperreflexia, tremor and fasciculations. Elevated T3/T4

Table 16.9 (continued)

Mimic	Diagnostic pointers
Benign fasciculation syndrome	Common reason for referral for ALS, and cause of anxiety. No weakness, atrophy, nor UMN sign. Negative electrodiagnostic testing. Benign prognosis
<i>Bulbar symptoms/signs alone</i>	
Mysthenia gravis and MuSK disease	Ptosis, extraocular muscle involvement, absence of UMN signs. Acetylcholine receptor and MuSK antibodies
Progressive supranuclear palsy	Parkinsonian signs, vertical eye movement abnormality
Bihemispheric strokes	No LMN sign. MRI brain
Polyneuritis cranialis, skull base lesions	Cranial neuropathies, MRI brain

gastrointestinal symptoms, elevated liver enzymes, anemia, and leukopenia. It is recommended that patients taking riluzole have blood counts and liver enzymes checked monthly for the first 3 months, then every 3 months for the remainder of the first year of treatment, and thereafter once annually.

Based upon demonstration of a significant reduction in functional decline over 6 months in a well-defined subgroup of early-stage ALS patients, edaravone was approved in May 2017 in the United States for treatment of ALS [37]. Edaravone is administered intravenously in a dose of 60 mg over 1 hour daily for 14 days initially, followed by a 2-week drug-free period. Subsequent cycles comprise similar dosing on 10 of 14 days, alternating with 2 drug-free weeks. Overall, edaravone is very well-tolerated. Hypersensitivity reactions including urticarial/angioedema, bronchoconstriction and even anaphylaxis are very rare, and are attributed to the added preservative sodium bisulfite in the edaravone preparation. The commonest side-effects of edaravone compared to placebo (with percent frequencies) include: contusion or bruising (19% edaravone vs 13% placebo), contact dermatitis (12% vs 4%), and eczema (7% vs 3%) [37].

As ALS progresses, the health care needs of the patient grow. In earlier stages of the disease, manual function, ambulation and speech/swallowing (in bulbar-onset cases) require assistance. As disease advances, nutritional and respiratory support become paramount. Multidisciplinary care once every few months may improve survival and quality of life in ALS, although evidence is inconclusive [38, 39]. Members of the team include a neurologist and/or a physiatrist, a nurse case manager, physical, occupational and speech therapists, a nutritionist, and a social worker. When possible, the team should also include or have access to a pulmonologist and respiratory therapist. Services of a gastroenterologist or general surgeon and an otorhinolaryngologist are sought when percutaneous endoscopic gastrostomy (PEG) and tracheostomy are considered, respectively. Consensus guidelines published by the American Academy of Neurology [40] for PEG and respiratory support are reproduced in Fig. 16.4. If there is weight loss or significant dysphagia, or if these problems are anticipated, PEG placement is preferred prior to forced vital capacity (FVC) decline below 50% of predicted. With declining ventilation, evidenced by symptoms, FVC, negative inspiratory force, and CO₂ accumulation, support is escalated. Initial non-invasive positive pressure ventilation for a few hours a

day gives way to more continuous support, and finally—if the patient chooses—to tracheostomy with full ventilatory support. For the majority of patients in the United States who choose not to receive tracheostomy, palliative management of dyspnea with opiates is strongly encouraged in terminal stages. During the course of ALS,

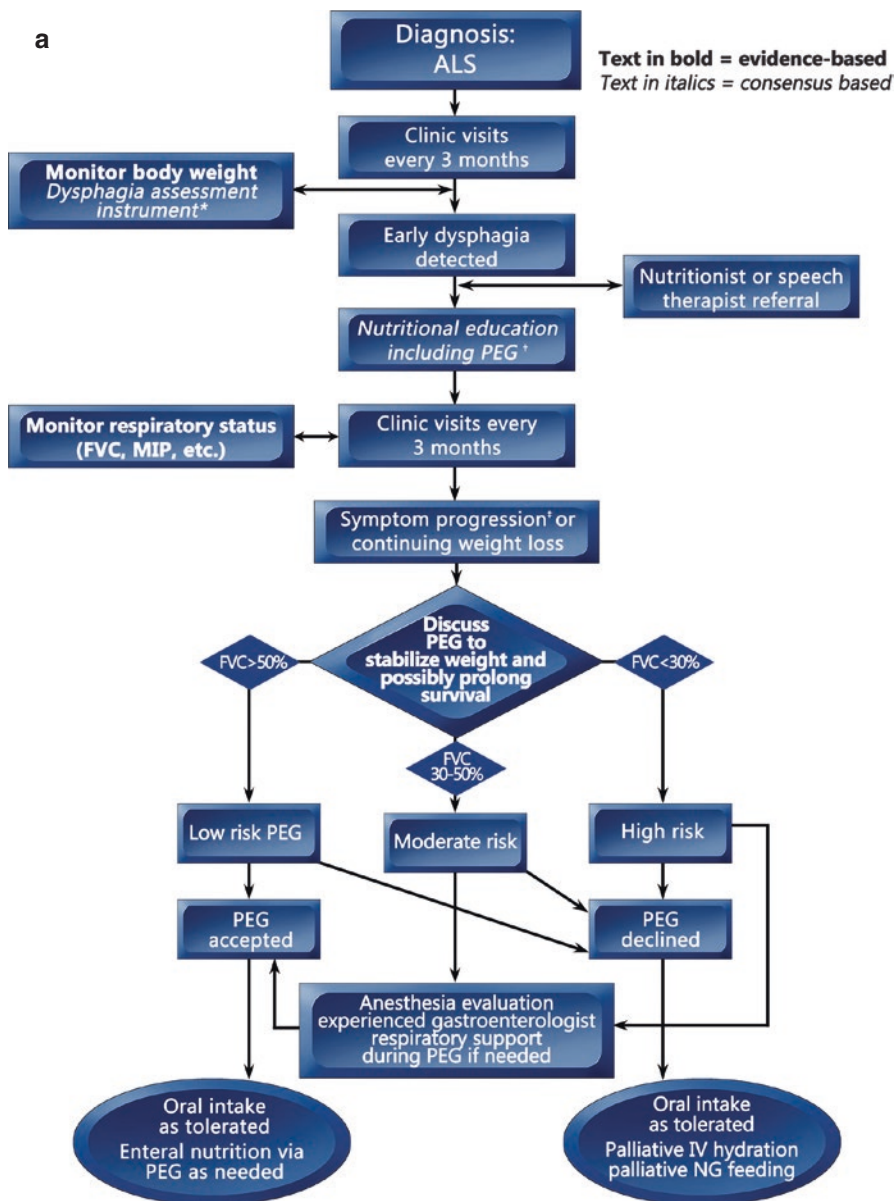


Fig. 16.4 Treatment of ALS (**a** and **b**). *PFT* pulmonary function tests, *PCEF* peak cough expiratory flow, *NIV* noninvasive ventilation, *SNP* sniff nasal pressure, *MIP* maximal inspiratory pressure, *FVC* forced vital capacity, *PEG* percutaneous endoscopic gastrostomy

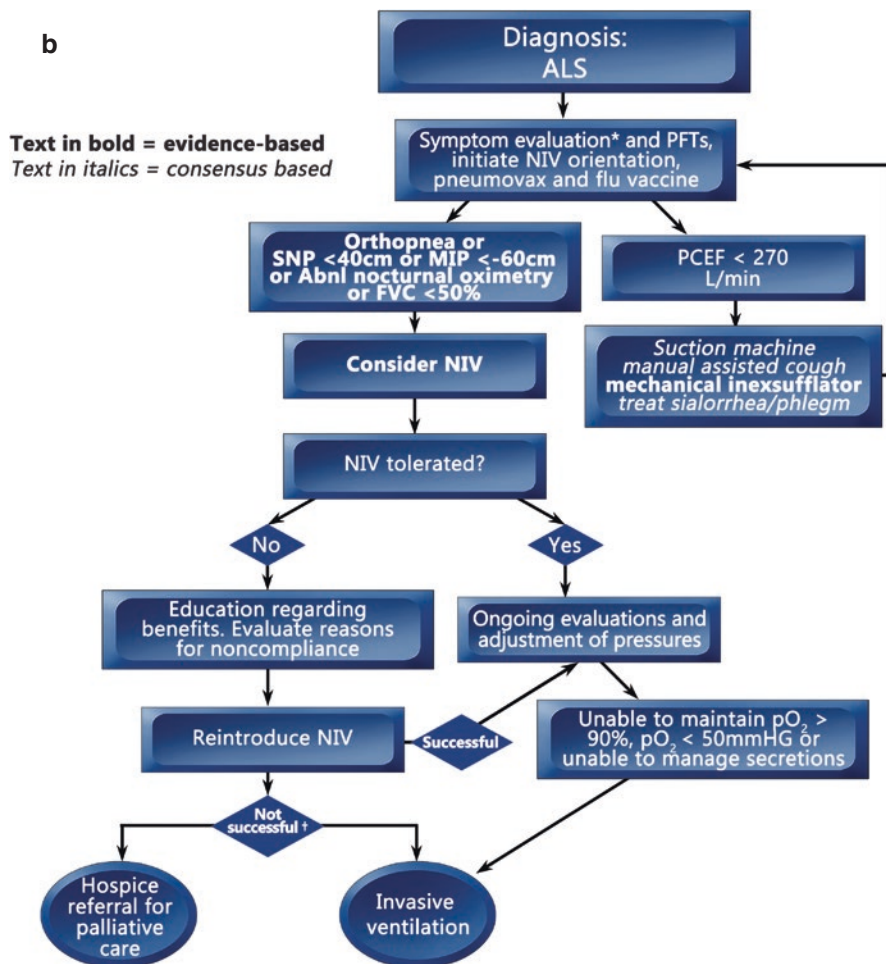


Fig. 16.4 (continued)

the patient may experience numerous additional symptoms that affect quality of life, and can be treated effectively [41]. These are summarized in Table 16.10.

Common ICD10 codes for polyneuropathy

E11.42 Type II diabetes with polyneuropathy

G60.3 Idiopathic progressive polyneuropathy

Numerous other codes are used for other specific polyneuropathies but will not be listed here because of space constraints

Common ICD10 codes for ALS

G12.21 Amyotrophic lateral sclerosis

G12.22 Progressive bulbar palsy

Table 16.10 Symptomatic treatment of ALS

Symptoms	Common approaches to management
Immobility	Physical therapy, orthotics, assistive devices, wheelchair
Loss of hand use	Occupational therapy, utensil modification, braces
Dysphagia	Speech therapy, dietary consistency modification, percutaneous endoscopic gastrostomy (PEG) tube
Sialorrhea	Anticholinergics, salivary gland botulinum toxin, radiation to salivary glands, suctioning
Thick secretions	Hydration, nebulizers, N-acetylcysteine
Pseudobulbar affect	SSRIs, dextromethorphan-quinidine
Dysarthria, anarthria	Speech therapy, communication aids, voice banking
Weight loss, malnutrition	Nutritional assessment, supplements, PEG tube
Dyspnea, poor cough	Non-invasive positive pressure ventilation (NIPPV), tracheostomy, suctioning, cough assist devices, respiratory therapy, opiates
Pain	Relieve cramps and spasticity, physical therapy, positioning and support, NSAIDs, neuropathic pain medications, opiates
Cramps	Sodium channel blockers (quinine, anticonvulsants, mexiletine)
Spasticity	Baclofen, tizanidine, diazepam, botulinum toxin injections
Depression, anxiety	Counseling, antidepressants, benzodiazepines
Fatigue	Address depression, discontinue Riluzole
Insomnia	NIPPV, positioning, treatment of pain, hypnotics
Constipation	Hydration, high fiber diet, laxatives, enema
Cognitive loss, behavioral problems	Psychiatric involvement, education, environmental changes, supervision, mood stabilizers, antidepressants, antipsychotics

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Chapter 17

Multiple Sclerosis

Le H. Hua

Clinical Pearls

- Diagnosis can be made with 1 MRI
- Rule out mimics to satisfy “no better diagnosis” caveat
- Treat early and assess for breakthrough disease regularly
- Distinguish between relapse (new or recurrent neurological symptoms lasting at least 48 h with objective signs such as new enhancing MRI lesion) and pseudo-relapses (recurrence of previous neurological symptoms in the setting of infections, metabolic disturbance, heat, or stress).

Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system. The early stage of the disease is predominately characterized by inflammation with limited neurodegeneration. As the disease evolves, inflammation decreases and disability is largely related to neurodegenerative processes [1].

MS affects approximately 400,000 individuals in United States and 2.5 million people worldwide. It is the leading cause of non-traumatic disability in young adults. Disease onset is generally between ages 20 and 40, but both pediatric and late-onset MS cases have been described [2]. Women are more affected than men, with a ratio approaching 3:1. There is greater prevalence in the latitudes farther from the equator, with risk of MS greatest during early life exposure to these higher latitudes. Environmental factors, such as vitamin D exposure, infectious agents

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like Epstein-Barr virus, and vascular risk factors including smoking, obesity, hypertension, hyperlipidemia, diabetes mellitus II, and high salt diet have been implicated in MS pathophysiology. Genetic and genome wide association studies (GWAS) have identified the risk alleles in the MHC-II gene, particularly HLA-DRB1*15:01, and over 100 different SNPs coding for proteins in the immune region [3]. Although the exact cause of MS is unknown, significant advances have been made in understanding disease pathogenesis and the interplay between genetic and environmental factors.

Clinical Manifestation (History and Physical Examination)

MS is a heterogeneous disease; individuals with MS can have different clinical courses, symptom manifestations, and treatment responses.

Multiple Sclerosis Classification

Relapsing-remitting MS (RRMS) is characterized by punctuated episodes of new or worsening symptoms, called clinical relapses, and periods of neurological stability. Progressive disease is characterized as gradual accumulation of disability irrespective of relapses, which can occur after an initial relapsing course (secondary-progressive (SP)) or from disease onset (primary progressive (PP)). The most recent classification schemes further modifies relapsing and progressive courses to assess disease activity and disease progression [4, 5].

Clinically isolated syndrome (CIS) is the first presentation of a typical demyelinating event, not yet meeting full MS diagnostic criteria. For CIS patients with an abnormal brain MRI at baseline, 80% will become clinically definite MS (CDMS) with a median time of 2 years, whereas only 20% of patients with normal baseline brain MRI will progress to CDMS [6]. Radiologically isolated syndrome (RIS) describes patients who undergo magnetic resonance imaging (MRI) for evaluation of something other than demyelinating disease with MRI findings suggestive of asymptomatic MS [7]. About 20% of patients with RIS will progress to CIS or CDMS in 5 years. This conversion rate increases to 80% if spinal cord lesions are present [8].

The clinical manifestations of MS are variable, as symptoms and initial presentation depend on lesion location within the neuraxis and the systems involved (Table 17.1). Typical clinical syndromes include optic neuritis, transverse myelitis, brainstem syndromes such as intranuclear ophthalmoplegia, and cerebellar syndromes. If the cervical spine is involved, patients may report Lhermitte's sign

Table 17.1 Clinical manifestations of MS

System	Signs and symptoms
Vision	Optic neuritis (painful vision loss, red desaturation), scotoma, diplopia
Brainstem	Intranuclear ophthalmoplegia, trigeminal neuralgia, facial weakness, dysphagia, dysarthria, slurred speech; vertigo
Cerebellar	Truncal ataxia, limb ataxia, scanning speech, tremor
Motor	Weakness, spasticity, gait disturbance, balance disturbance, motor fatigue
Sensory	Numbness and tingling, loss of vibration
Bladder/bowel	Frequency, urgency, hesitancy, retention, incontinence
Cognitive	Poor attention, fatigue, slow processing speed

(tingling sensation radiating down the arms or spine upon neck flexion). Patients commonly have brisk reflexes indicating injury to the upper motor neuron system. Uhthoff's phenomenon, the worsening of symptoms with increased temperatures, is common.

Diagnostic Approach

MS is a clinical diagnosis based on key clinical history and objective evidence supporting a MS diagnosis (Fig. 17.1).

Laboratory

There is no specific laboratory criteria to diagnose multiple sclerosis, however mimics should be considered and ruled out appropriately based on clinical suspicion. Cerebral spinal fluid (CSF) studies can be supportive for MS, but are not necessary for diagnosis. It should be performed to rule out other processes (infections, neoplasms) based on clinical suspicion. Typical tests include: cell count and differential, total protein, glucose, oligoclonal bands via isoelectrical focusing, IgG Index and IgG synthesis rate. Others tests such as cytology and flow cytometry, culture, viral titers and PCR, VDRL can be obtained as indicated. Patients with MS will typically have oligoclonal bands and elevated IgG index or IgG synthesis rate, though about 20% of patients with MS have negative CSF findings. Oligoclonal bands are not specific for MS and can be found in other disease processes [9]; and oligoclonal bands in both the serum and CSF should raise suspicion for an alternate diagnosis.

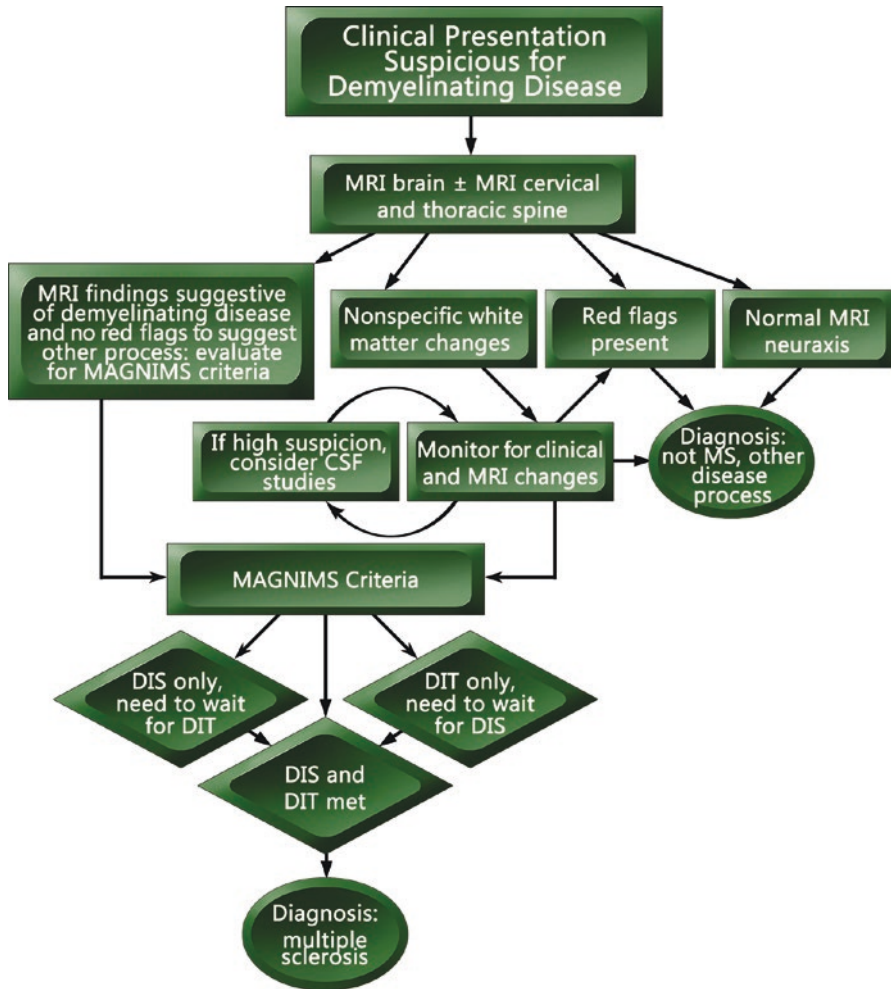


Fig. 17.1 Diagnostic care path for MS

Imaging

The use of MRI has facilitated the diagnosis of MS, decreasing utility of laboratory and CSF studies and evoked potentials, especially if classic “Dawson fingers” are seen (Fig. 17.2). Lesions are typically ovoid and greater than 3 mm, and periventricular lesions are typically perpendicular to the long axis of the lateral ventricles. MRI also helps identify alternate diagnoses such as cerebrovascular ischemia or neoplasms. Normal MRI of the neuraxis indicates a non-MS process and the need to search for an alternate diagnosis. Nonspecific white matter changes found with migraine vasculopathy or small vessel disease are sometimes misdiagnosed as MS. The addition of spinal cord imaging can be helpful especially in patients over age 50 [10].

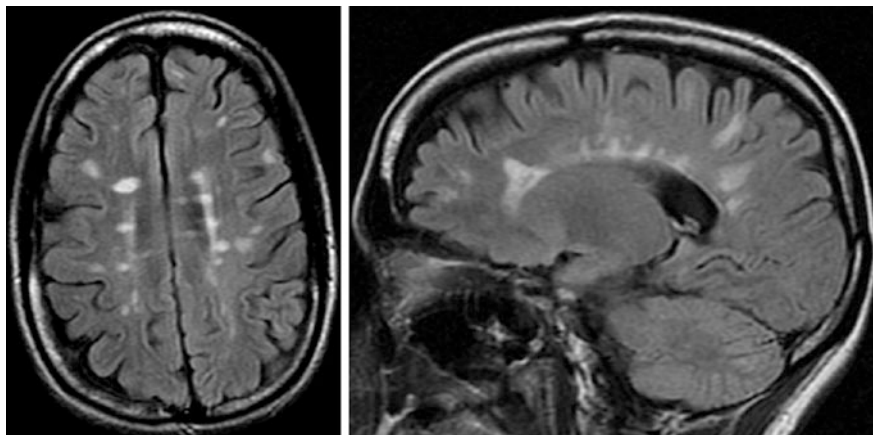


Fig. 17.2 Typical MRI appearance of MS. Axial and sagittal MRI FLAIR sequences with periventricular and juxtacortical lesions, with classic Dawson's fingers (periventricular ovoid FLAIR hyperintensities radiating perpendicularly from lateral ventricles and involving the corpus callosum on sagittal MRI)

Electrophysiology

Evoked potentials lack sensitivity and specificity, but can be supportive in instances when one is unable to obtain MRI. Visual evoked potentials can demonstrate injury to the visual system and are often delayed when optic neuritis is present. Similarly, somatosensory and brainstem auditory evoked responses can demonstrate injury to the anterior lateral sensory pathways from the arm or leg and the vestibular-cochlear pathways, respectively.

Genetics

Genetic testing in MS is not helpful in the clinical management of patients with MS. Genetic and GWAS studies however have contributed to advancing our understanding of the pathophysiology of MS and are being explored as potential biomarkers for treatment.

Other Ancillary Tests

Optical coherence tomography (OCT) has potential to become a useful tool to monitor disease progression in MS. Patients with MS typically show peripapillary retinal nerve fiber layer (RNFL) and retinal ganglion cell layer (GCL) thinning [11]. It may also confirm evidence of prior optic neuritis [12].

Diagnosis Criteria

The 2010 McDonald Criteria (Table 17.2) for MS requires a clinical presentation of 2 attacks (or relapses) with objective evidence of dissemination in space (DIS) and dissemination in time (DIT) [13]. A relapse is an acute episode of neurological change lasting for at least 24 hours in the absence of fever or infection. MRI is often used for DIS and DIT based on 2016 MAGNIMS criteria (see Table 17.2) [14–17]. DIS is defined as lesions present in 2 out of the 5 typical locations for MS: periventricular, juxtacortical and/or cortical, infratentorial, spinal cord or optic nerve. At least 3 lesions should be present in the periventricular region for this criterion to be fulfilled, all other areas only require 1 lesion. DIT can be met by presence of an asymptomatic gadolinium enhancing lesion or a new lesion on subsequent MRI at any time.

The diagnosis of MS is made when both DIS and DIT criteria are met, and both can be satisfied using only one MRI scan. If only one criterion is met, the patient has possible multiple sclerosis. Patients who present as CIS (one attack with objective evidence of one lesion) need to be monitored for a second attack that would meet criteria for MS. Primary progressive MS is defined as 1 year of clinical progression to fulfill DIT criteria, and two of three of the following: MRI brain findings that meet DIS criteria, two lesions in the cord, or positive CSF. A key caveat of the McDonald criteria is the exclusion of other disease processes that may better explain the clinical presentation (Table 17.3).

Differential Diagnosis

Many disease processes can present similarly and/or can be associated with white matter changes on MRI. The most common disorders are listed in Table 17.4 with clinical features that would be considered red flags.

Table 17.2 2016 MAGNIMS MRI criteria

<i>DIS</i>
Lesions present in 2 out of the 5 locations: periventricular (3 or more lesions), juxtacortical/cortical, infratentorial, spinal cord and optic nerve
<i>DIT</i>
Presence of an asymptomatic gadolinium enhancing lesion or a new lesion on subsequent MRI at any time

Table 17.3 2010 McDonald criteria

≥ 2 clinical attacks, ≥ 2 objective lesions → MS
≥ 2 clinical attacks, 1 objective lesion → need DIS
1 clinical attack, ≥ 2 objective lesions → need DIT
1 clinical attack, 1 objective lesion → CIS, need both DIS and DIT
Progressive course over 1 year AND 2 of 3 of the following (MRI brain meet DIS, 2 spinal cord lesions, positive CSF) --> PPMS

Table 17.4 Differential diagnosis of MS

Disorders	Clinical features
<i>Disorders with similar symptoms</i>	
Neuromyelitis optica (NMO)	Longitudinally extensive transverse myelitis (greater than three spinal cord segments) and/or optic neuritis, in the presence of normal MRI brain. Positive NMO antibody titer
Para/post infectious transverse myelitis	History of infection temporally correlated to symptoms of transverse myelitis. Usually monophasic
Acute demyelinating encephalomyelitis (ADEM)	Multiple, simultaneously enhancing demyelinating lesions, with encephalopathy and seizures
Chronic relapsing Inflammatory Optic Neuritis (CRION)	Recurrent optic neuritis with normal MRI brain and spinal cord. Negative NMO antibody titer
Neurosarcoidosis	Meningeal and nodular enhancement, “string on bead” pattern in spinal cord, granulomas on biopsy
Systemic lupus erythematosus, Sjogren’s syndrome	Systemic inflammatory signs, arthralgias, malar rash, dry mouth, dry eyes, elevated serum auto-antibodies
Behcet’s disease	Oral and genital ulcers, encephalopathy
Vitamin B12/copper deficiency	Longitudinal posterior column myelopathy, cognitive dysfunction, megaloblastic anemia
HTLV-1	Slowly progressive myelopathy
Lyme disease	Endemic area and history of tick bite, positive lyme serologies
Fibromyalgia	Diffuse generalized pain, fatigue, cognitive complaints
<i>Disorders with white matter abnormalities</i>	
Migraines	Subcortical lesions on MRI
Vascular: small vessel disease, CNS vasculitis	Microvascular ischemic changes, cardiovascular risk factors, abnormal cerebral vessel imaging
Susac disease	Small vessel arteriopathy with hearing loss, vision changes, encephalopathy. MRI with multiple strokes, central involvement of corpus callosum
Cerebral autosomal dominant arteriopathy with stroke like episodes and leukoencephalopathy (CADASIL)	Genetic disorder with strokes, migraines and dementia, strong family history, MRI with increased T2 signal of temporal tips
Leukodystrophies	Subcortical confluent white matter changes, symmetric
Neoplasms	Persistent enhancement, surrounding edema, mass effect, expanding lesions

For late-onset MS (patients older than 60 who present with new symptoms and meet MS diagnostic criteria, rather than delayed diagnosis of MS in persons with symptoms presenting earlier in life), the differential diagnosis is similar, however processes that are more common in older individuals such as degenerative spinal disc disease, urinary dysfunction, cerebrovascular ischemia, and neoplasms, can complicate the diagnosis.

Therapeutics

Most patients with MS and patients who are considered CIS with a high risk of progression should be started on disease modifying therapies (DMTs). There are 15 FDA-approved DMTs for MS, and are available in injection, oral, and intravenous forms. All currently approved therapies demonstrate reduction in annualized relapse rate, MRI lesions, and disability. Early initiation of treatment decreases disability progression and improves quality of life. The choice of the right treatment for the right patient can be difficult, with the need to balance efficacy, side effects, and safety. As MS is a heterogeneous disease, each patient's treatment should be individualized based on patient factors (degree of MS disease activity, preference for DMT administration, and risk tolerance level) and comorbidities. In general, goals of treatment are to stop clinical relapses, development of new or enlarging MRI lesions, and disease progression. This has become known as the “no evidence of disease activity” (NEDA) target. If patients show signs of breakthrough disease then changing DMT is often warranted, balancing safety and patient factors. Any agent can be considered for initial use; however, the more efficacious and high-risk medications are generally reserved as second line agents or for highly active patients (Fig. 17.3).

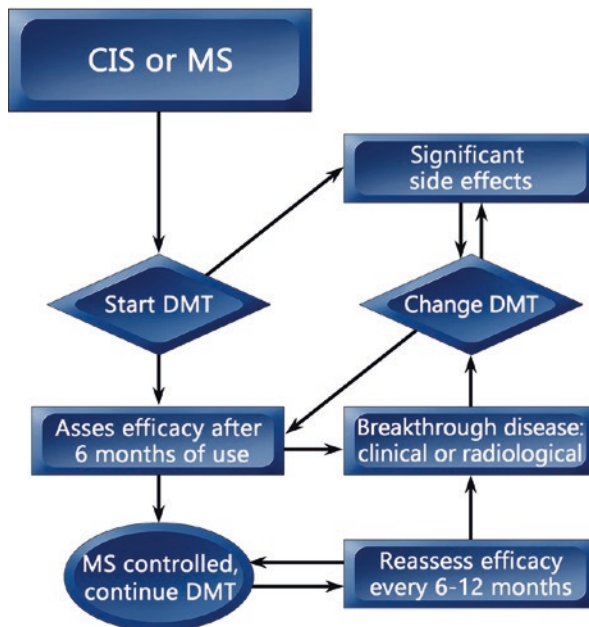


Fig. 17.3 Treatment care path for MS

For patients already demonstrating a progressive course, it is debatable if the current DMTs that primarily target inflammation are beneficial. At this time, with the exception of mitoxantrone and ocrelizumab, the data on currently commercially approved DMTs from progressive trials have not met efficacy endpoints. Explanations may be due to inadequate biomarkers for progression versus different pathophysiological mechanisms for progression unrelated to inflammation.

As patients age, other comorbidities may limit DMT choices, such as cardiac conditions, cancer requiring chemotherapy, or development of disabilities increasing risk of infections. Additionally, many of the pivotal studies for DMTs excluded patients greater than 55 years of age, therefore safety in this older population is limited to post marketing analysis. For patients who are diagnosed after the sixth decade of life, benefits of starting DMT are balanced by risks of side effects and comorbid conditions. Patients who are diagnosed later in life may have a milder course of MS with disease onset occurring much earlier in life but escaping diagnostic attention until an MRI is performed, and may not require DMT. Other patients have bona fide late-onset MS and continue to demonstrate clinical and radiological evidence of disease activity, therefore warranting DMT to control inflammatory disease activity.

Disease Modifying Therapies

Interferon-beta

There are several different formulations of interferon beta which vary in dosing frequency: interferon beta-1b administered subcutaneously every other day, interferon beta-1a administered intramuscularly once a week or subcutaneously three times per week, and peginterferon-1a administered subcutaneously every 2 weeks. Interferons are thought to have anti-inflammatory and immunodulatory effects by inhibiting T-cell activation and proliferation, inducing apoptosis of autoreactive T cells, cytokine modulation and enhancing anti-inflammatory responses, and inhibition of leukocyte migration across the blood brain barrier [17]. Common side effects from the interferons include flu-like symptoms, injection site reactions, fatigue, depression, leukopenia and transaminitis.

Glatiramer Acetate

Glatiramer acetate is administered subcutaneously and available as either 20 mg daily or 40 mg three times per week. The mechanism of action of glatiramer acetate accounting for its clinical benefit in MS is incompletely understood but is hypothesized to involve competition with myelin autoantigens at the major histocompatibility complex class II binding site on antigen presenting cells, induction of antigen-specific Th2 T-cells leading to bystander suppression of inflammation, and stimulation of neurotrophic factor secretion by immune cells [18]. Common side effects are injection site reactions, immediate post-injection reactions, and lipoatrophy.

Fingolimod

Fingolimod was the first oral therapy to be approved for RRMS. It is a once daily pill that binds to and modulates the sphingosine 1 phosphate (S1P) receptor. By binding to the S1P receptors, fingolimod is thought to sequester lymphocytes in lymph nodes, thus decreasing the inflammatory response in MS, although other mechanisms may underlie fingolimod's potential for neuroprotection, as fingolimod crosses the blood brain barrier, and S1P and S1P receptors are found in the CNS. S1P receptor interaction also accounts for the cardiovascular (bradycardia, slowed atrioventricular conduction, increased blood pressure), pulmonary, and macular edema side effects for fingolimod [19]. Other side effects include transaminitis, reduced protection against viral infections, and possible risk of malignancy. Because of the cardiac effects, fingolimod requires at least a 6 h first dose observation. Regular examinations for macular edema are also required before starting medication, after 3–4 months and annually thereafter as needed.

Teriflunomide

Teriflunomide is a once daily pill, and is an active metabolite of leflunomide, which is approved for use in rheumatoid arthritis. It is available in 7 and 14 mg doses. Teriflunomide reversibly inhibits dihydroorotate dehydrogenase which is involved in new pyrimidine synthesis for rapidly dividing cells, while preserving the salvage pathway for resting lymphocytes [20]. This is thought to reduce T and B cell proliferation and have anti-inflammatory effects. Common side effects are hair thinning, gastrointestinal disturbance (diarrhea, nausea), headaches, and transaminitis. This medication is considered teratogenic even if the patient is male, and therefore counselling regarding contraception is imperative. This medication may still be detected years after use and therefore elimination methods with activated charcoal or cholestyramine are available for rapid “wash out”.

Dimethyl Fumarate

Dimethyl fumarate (DMF) is an oral pill taken twice daily. Its immunomodulatory effects are unknown, but studies have demonstrated reduction in peripheral blood mononuclear cells and cytokine shifts from Th1 pro-inflammatory cytokines to Th2 anti-inflammatory cytokines. DMF also activates transcription of the nuclear (erythroid-derived 2) related factor (Nrf2) pathways, and thus has antioxidant and possible neuroprotective effects [21]. Side effects with DMF include flushing and gastrointestinal symptoms (diarrhea, abdominal cramping, nausea), which decreases after the first 2 months of use. Other side effects include transaminitis, lymphopenia, and increased risk of infections.

Natalizumab

Natalizumab is a monoclonal antibody directed at alpha 4 integrin cellular adhesion molecule on activated T cells, preventing binding to vascular endothelium and thus reducing activated T cells' ability to cross the blood brain barrier. It is administered in doses of 300 mg intravenously every 4 weeks. Use of natalizumab is limited by an increased risk of progressive multifocal leukoencephalopathy (PML) in certain patients. The risk of PML increases with duration of use (greater than 2 years), presence of JC virus antibody, and previous exposure to immunosuppressants. For patients who are anti-JCV antibody negative, monitoring every 3 months is recommended for risk surveillance. PML may be identified on MRI prior to clinical signs and symptoms, and early detection is associated with improved outcomes. Therefore, in patients who are at high risk of PML and natalizumab is still the best therapeutic choice, MRI monitoring should occur every 3–4 months.

Alemtuzumab

Alemtuzumab is a monoclonal antibody directed against CD52, which is a glycoprotein found on mature lymphocytes. It is administered initially as 12 mg/day intravenously for a 5 day infusion, with subsequent 3 day infusions yearly. Alemtuzumab effectively depletes T and B lymphocytes and monocytes. It is considered an immunomodulatory agent, as lymphocytes re-populate with a different repertoire (early B cell and monocyte repletion, delayed T cell repletion). This disturbed balance appears to have significant effects of relapses and disease progression, with a majority of patients requiring only two treatments [22].

The altered lymphocyte repertoire increases risk of possible secondary autoimmune conditions including thyroid disease (34%), immune thrombocytopenia (2%) and antibody mediated glomerular nephropathies (0.3%). Other side effects include infusion related reactions (headache, rash, nausea, pyrexia), infections, serious life threatening infections in ~3%, and increased risk of malignancies. Patients receiving alemtuzumab also need to be enrolled in a risk-monitoring program with monthly labs until 48 months after the last infusion and require anti-viral prophylaxis against herpes viral infections until CD4 counts normalize.

Mitoxantrone

Mitoxantrone was the first approved therapy for progressive MS to date. It is anthra-enedione chemotherapeutic agent that causes generalized immunosuppression. It is administered intravenously 12 mg/m² every 3 months, with a total dose limit of eight courses. It is efficacious in highly active MS patients and reduces rate of disability progression in SPMS. Use of mitoxantrone is severely limited by cardiac toxicity and secondary leukemia.

Daclizumab

Daclizumab is a humanized anti-CD25 monoclonal antibody, which modulates interleukin-2 signaling, and leads to expansion of CD56bright natural killer cells, inhibition of T cell activation, and reduces development of lymphoid tissue inducer cells [23]. It is 150 mg subcutaneous injection given monthly. Side effects include other immune mediated disorders with skin reactions and lymphadenopathy as the most common and liver toxicity including autoimmune hepatitis. Use of daclizumab requires a risk monitoring program to evaluate liver function monthly, while on medication and up to 6 months after treatment discontinuation. Other adverse effects of note are nasopharyngitis, upper respiratory infections and depression.

Ocrelizumab

Ocrelizumab is a humanized anti-CD20 monoclonal antibody targeting B cells, which disrupts several immune processes in multiple sclerosis such as antigen presentation, autoantibody production, and cytokine regulation. It is approved for both relapsing and primary progressive MS. It is administered as a 600 mg intravenous infusion every 6 months (with the first dose split into two infusions two weeks apart). Side effects include infusions reactions, infections and potentially malignancy. It is a highly efficacious option and should especially be considered for very active patients who are also JCV antibody positive.

Relapse Management

MS relapses are typically treated with a course of high dose steroids, usually 1000 mg methylprednisolone intravenously for 3–5 days. Some studies have shown that high dose oral equivalents are equally efficacious compared to intravenous formulations [24]. Although steroids do not alter the overall disease course or degree of recovery, they may accelerate recovery time [25]. Steroids have risks of elevation in blood glucose, osteoporosis, cataract formation, mood effects, gastritis, insomnia, increased infection and avascular necrosis. For severe relapses where steroids are insufficient, plasma exchange can be considered [26].

It is important to confirm clinical relapse from MS based on objective findings as there are implications in terms of changing DMT based on NEDA goals and escalating DMT inappropriately. Pseudo-relapses are the recurrence of previous neurological symptoms triggered by infections, metabolic disturbance, heat, or stress. Pseudo-relapses should not be treated with steroids, but attention should be focused on patient education, reassurance, and addressing the underlying trigger. It is also important to rule out new neurological symptoms from other processes such as degenerative disc disease, ischemia, peripheral neuropathy, etc.

Symptom Management

Equally important in the management of patients with MS is symptom management. Gait difficulty, balance disorders, depression, bladder and bowel dysfunction, spasticity, pain syndromes (trigeminal neuralgia, migraines and headaches, dysesthesias, neuropathic pain), fatigue, and cognitive changes are common. The treatments of these symptoms are similar to other medical conditions. Dalfampridine is an approved therapy to help with walking and walking speed.

Comorbid conditions can also contribute to symptoms. Diabetes can lead to neuropathic pain and bowel dysfunction from gastroparesis. Cognitive changes may be related to pseudo-dementia of depression, fatigue, medication side effects, development of neurodegenerative cognitive disorders such as Alzheimer's disease, or changes from MS. Degenerative disc disease can lead to radicular symptoms, gait impairment, pain syndromes, or bladder and bowel dysfunction.

ICD-10

G35 multiple sclerosis

G36 other acute disseminated demyelination

G37 other demyelinating diseases of central nervous system

G37.9 demyelinating disease of the central nervous system, unspecified

Disclosures Dr. Hua reports personal compensation for serving on scientific advisory boards and consulting for Genzyme, Genentech, EMD Serono, Novartis and TG Therapeutics and as a speaker for Teva, Genzyme, Biogen, and EMD Serono.

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Chapter 18

Epilepsy in the Elderly

Olesya Grinenko and Imad Najm

Clinical Pearls

- First seizure in an older patient: think structural abnormalities and get high resolution imaging study (MRI)
- Fluctuating level of consciousness in an older patient with baseline cognitive dysfunction: rule out epileptic seizures through short or long EEG recordings
- Diagnosis of epilepsy is either suspected or confirmed: start an anti-epileptic medication. There is Level A evidence of efficacy for three AEDs in the elderly: Gabapentin and Lamotrigine, Levetiracetam.
- If two or more AEDs failed consider presurgical evaluation.

Introduction

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure. An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [1]. Therefore, epilepsy exhibits itself episodically through a set of well-defined symptoms and signs and its diagnosis is only confirmed through electroencephalographic (EEG) recordings.

Epilepsy affects between 1 and 2% of the general population. Incidence and prevalence of epilepsy increases with age. According to population-based studies cumulative incidence rises from 1.7% at age 50 to 3.4% at age 80 [2]. Among

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Medicare beneficiaries, the average annual prevalence and incidence rates were 10.8/1000 and 2.4/1000 respectively [3]. The prevalence and incidence rates are even higher (7.9 and 19.3 per 1000 person-years) in low-income elderly population and in patients with comorbid conditions such as stroke, dementia, hypertension, as well as in non-Hispanic and black population [4].

Etiologies and Risk Factors

The rate of symptomatic causes of epilepsy is high in older patients. Cerebrovascular etiologies are prevalent and account for about 50% of all symptomatic epilepsies in elderly. Less common causes include traumatic brain injury, neoplastic lesions, metabolic disorders, and dementia [5–7]. Acute cerebrovascular events are also predominant causes of a single seizures. Other causes include alcoholism, polytherapy, neurodegenerative diseases, HIV infection [8].

Following stroke, epilepsy develops in ~2.5% of patients and a single epileptic seizure occur in ~9%. Risk is higher in patients with hemorrhage and cortical location of infarct [9–11].

Epilepsy and stroke has bidirectional relationships: elderly patients with epilepsy has increased risk of stroke (2.89 relative hazard) [12]. They also have higher rate of somatic comorbidities such as hypertension, hyperlipidemia, myocardial infarction, diabetes and arteriosclerosis [13]. In the Rotterdam study, total cholesterol level and presence of left ventricular hypertrophy were correlated with epilepsy even when patients with prior stroke were excluded from analysis [14]. These studies support indications to evaluate and manage cardiovascular risk factors in elderly with epilepsy to prevent future stroke.

In patients with Alzheimer's disease (AD), epilepsy may occur at any stage of the disease (and it may even be prodromal). Case series of late onset temporal lobe epilepsy that were followed by an Alzheimer's disease diagnosis 4–7 years later was reported [15]. Seizure incidence is similar in mild and moderate AD [16], however, recognition of seizures is more difficult in patients at late stage of the disease. In addition, patients with epilepsy has greater degree of cognitive impairment in younger age.

Traumatic brain injury (TBI) is the presumed cause of epilepsy in 5–10% of elderly patients. Risk factors for developing epilepsy after TBI are brain contusion or intracranial hemorrhage. The risk is usually higher during first 6 months after trauma, however it remains elevated more than 10 years later [17]. In a population-based study, the risk of epilepsy development after TBI was significantly higher in patients with brain contusion, subdural hematoma, skull fracture, loss of consciousness or amnesia for more than 1 day, and age 65 years and older [18].

Brain neoplasms are diagnosed in up to 33% of elderly with epilepsy [19]. According to the central brain tumor registry of the United States (2012), most frequent tumor diagnosis in patients with epilepsy 65 years and older are meningioma and glioblastoma. Benign neoplasms are less common in this age group.

Nevertheless, epilepsy due to dysembryoplastic neuroepithelial tumors and low grade astrocytomas and oligodendrogliomas are also reported [20].

Clinical Manifestations

Epileptic seizures in elderly are commonly less elaborate and brief [21, 22], however, can be accompanied by long episodes of postictal confusion [23].

In patients with dementia [24, 25] and AD [26], epileptic events commonly characterized only by episodes of transient cognitive dysfunction. This subtle presentation may lead to delay in diagnosis [27].

Non-convulsive status epilepticus is represent another challenge for epilepsy management in elderly [28–30]. It can manifest as absence status in patients with pre-existing idiopathic generalized epilepsy, or as complex partial status in patients with focal brain lesions. It is also frequently reported as cause of consciousness alteration in critically ill patients. *De novo* non-convulsive status can be precipitated by benzodiazepine withdrawal.

The rate of new onset status epilepticus is twice higher in elderly compare to general population [31]. In a prospective study 32% of epilepsies were presented as new onset cluster of seizures and/or status [32]. Generalized convulsive status was most frequent followed by *epilepsia partialis continua*, non-convulsive and myoclonic status. More than half of these patients had acute symptomatic etiology, followed by cryptogenic and remote symptomatic.

Tips for Clinical Diagnosis of Epilepsy

History

A detailed history is of paramount importance in the process of assessing patients with seizures. Patient and family history taken should identify risk factors for epilepsy (or clues to the possibility of non-epileptic spells), possible causes for the seizures (see Tables 18.1 and 18.2), and location/severity of the disease.

Table 18.1 Risk factors/causes of epilepsy

Ischemic or hemorrhagic brain lesions
Head trauma with loss of consciousness
Brain neoplasm
Central nervous system (CNS) infection
Chemotherapy
Family history of epilepsy
Prenatal and/or perinatal complications
Delay in major developmental milestones
Childhood febrile seizure

Table 18.2 Medical/neurological conditions with seizure-like episodes

Cerebrovascular disease/transient ischemic attack
Cardiac or vascular disease
Diabetes mellitus
Dehydration
History of hypotension
Sleep disorders/parasomnias
Some metabolic diseases
Movement disorders
History of migraine and its type
Lung disease

Seizure Semiology

Detailed Clinical Seizure/Spell Description

The clinical seizure description should be gathered from the patient first and then from witnesses (usually family members). The first piece of information needed is in regards to the level of consciousness of the patient during the seizure. Some seizures (also known as simple partial seizures) consist of sensory and/or motor manifestations without loss of consciousness and are not associated with ictal amnesia. Other seizures (also known as complex partial seizures) consist of loss of consciousness with ictal amnesia. The information about the simple partial seizures is usually provided by the patient. Therefore, the patient should be allowed to describe everything he/she knows about the seizure without any intervention from the witnesses. Following the description of the seizure by the patient, witnessed accounts should be gathered with special emphasis on the initial manifestations of the seizure that are noted. There should be investigation of any focality of the seizure; for example, initial focal motor manifestations that may include clonic movements of the face, hand or arm.

The Presence of an Aura

An aura is defined as a subjective sensation that precedes and marks the onset of a neurological condition, particularly an epileptic seizure (epileptic aura) or migraine (migraine aura). Epileptic auras tend to be very short in duration (less than a minute), may occur in isolation or may be followed by a clinical seizure. The identification of an aura in the setting of a suspected epileptic seizure is important as it highly suggests that the epilepsy is focal, and may lead to additional details on the side and/or location of the epilepsy.

Circumstances in Which the Seizure Occurred

The goal should be to identify potential triggering or provoking factors. These may include but are not limited to the following details: sleep deprivation, excessive consumption of alcohol or drugs, ingestion of potentially pro-epileptic prescription medications, unusual stressors (physical or mental).

The Time of Occurrence of the Spell

Some frontal lobe seizures occur more often during sleep.

Seizure Severity

Notation should be made of seizure generalization, tongue biting (including its side when pertinent), sphincter incontinence and history of status epilepticus (seizures with long duration, or multiple seizures without recovery of consciousness).

Seizure Duration

The majority of uncomplicated epileptic seizures last less than 2 min.

Postictal Manifestations

Notation should be made of any postictal neurological deficit (speech, motor and/or sensory) and the time from the seizure to full recovery of all functions to baseline.

Neurological Examination

The main goals of the neurological examination in patients presenting with the chief complaint of seizures/convulsions or epilepsy are to establish a baseline for the general cognitive and neurological functions, and to assess for possible medication side effects. Of particular interest is the screening for focal neurological deficits. Cognitive impairment in elderly patients may compromise history taking and a simple screening with mini-mental state examination should be considered. The assessment should include: (1) Mental state testing, (2) Speech assessment, (3) Cranial nerves assessment, (4) Motor and sensory functions examinations, and (5) Gait and balance testing.

Diagnostic Approach

The goals of the evaluation of patients with suspected epilepsy and those presenting with the chief complaint of seizures, convulsions, spells, etc., are:

- Confirm the diagnosis of epilepsy or develop a reasonable suspicion that the patient has epilepsy: *epileptic vs. nonepileptic seizures*
- Define the type of epilepsy: *focal vs. generalized* → *appropriate choice of AED*
- Define the cause whenever possible: *provoked, unprovoked, symptomatic, etc.*

Electrophysiology

Outpatient EEG may support the diagnosis of epilepsy through the recordings of spikes or sharp waves. The presence of epileptiform activities (spikes/sharp waves) may help in assessing the risk of recurrent seizures in patients presenting after only one seizure. A meta-analysis showed that the risk of seizure recurrence in the setting of a normal EEG is 27.4%, while the risk of seizure recurrence in patients with spikes on EEG is 49.5%. In addition, the distribution of epileptiform discharges in the EEG may point to the diagnosis of focal or generalized epilepsy. Epileptiform activity should be distinguished from normal physiological variants like mid-temporal delta of drowsiness and SERDA that are frequent in the elderly patients [33]. Additionally, non-epileptiform abnormalities are frequent in this age group and often lead to misdiagnosis of epilepsy [34]. Moreover, outpatient EEG has limited diagnostic value: interictal epileptiform abnormalities can be captured only in one third of patients [35].

Prolonged Video EEG monitoring can increase diagnostic yield. Interictal epileptiform abnormalities can be captured in 70–80% of patients with epilepsy [36]. However, seizure recording is important to rule out behavioral non epileptic spells that may be confused with epileptic seizures. According to different reports from 30 to 55% of elderly patients admitted for diagnostic video-EEG are having non-epileptic seizures [22, 35–38]. It is important to note that one third of these patients also had interictal epileptic discharges. Prolonged video EEG monitoring is also recommended to rule out non-convulsive status epilepticus that usually manifests as decreased level of consciousness, aphasia, altered mental status or psychosis and can be misdiagnosed with delirium or coma [30, 39].

Therefore, video EEG monitoring should be considered for:

1. Differential diagnosis between epileptic and non-epileptic seizures
2. Epilepsy diagnosis in patients with altered mental status
3. Assessment of seizure burden and efficacy of antiepileptic treatment
4. Presurgical evaluation (in particular in patients with brain lesions that could be amenable to surgical treatment)

Imaging

There are no agreed-upon recommendations for the imaging of patients with epilepsy. MRI should be considered the diagnostic method of choice (in particular those undergoing surgical evaluation) for the identification of potentially epileptic lesions. MRI techniques provide the most detailed information on the anatomy of the brain and aid in the detection of lesions that otherwise may have gone unnoticed/undetected.

The caveat is that the presence of an MRI abnormality does not necessarily mean that it is the cause of the epilepsy. It is necessary to establish with clinical and

neurophysiological data whether a given lesion is likely to be responsible for the seizures [40]. At Cleveland Clinic, we use MRI in all patients with suspected focal epilepsy and in those patients evaluated for epilepsy surgery.

Other Ancillary Tests

Other tests such as electrocardiography, blood tests, lumbar puncture, assessment of risk factors for stroke, neuropsychological testing, sleep study should be considered depending on clinical circumstances.

Psychiatric Comorbidities and Quality of Life

Elderly patients with epilepsy have high rate of depressive disorders, anxiety and psychotic disorders [41, 42]. Psychiatric comorbidities can compromise epilepsy treatment adherence as well as quality of life even in those who have achieved epilepsy-freedom [43–45]. The goals of psychiatric treatment in these group of patients are symptom remission; improved function, including optimal participation in epilepsy management; and optimal quality of life. Achieving these goals requires first diagnosis of the psychiatric disorder(s) when present, implementation of adequate treatment, provision of follow-up to ensure continuation and maintenance of improvement, and real-time self-assessment to promote continued improvement of care.

Diagnostic Criteria

Recently, the International League Against Epilepsy (ILAE) revised the definition of epilepsy [46]. In the new definition, epilepsy is a disease of the brain defined by any of the following conditions:

- At least two unprovoked (or reflex) seizures occurring >24 h apart
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
- Diagnosis of an Epilepsy Syndrome

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

Therapeutics

Medical Treatment of Epilepsy

The goals of medical treatment with AEDs were defined by the NIH Curing Epilepsy conference as follows: (1) Complete seizure control, (2) No side effects, and (3) Control of comorbid conditions.

The treatment of patients after the first seizure is an area of debate. But multiple studies assessing the risks of seizure recurrence after a first seizure identified possible risk factors that would increase the incidence of seizure recurrence following the first seizure. These risk factors include: The type of seizure: focal onset seizures, focal abnormalities on the neurological examination, focal epileptiform EEG abnormalities, and focal (mainly) cortical lesion on MRI. The recommendations for treating a patient after the first seizure are summarized in Table 18.3.

Medical treatment is generally recommended in the majority of patients when the diagnosis of epilepsy is suspected or confirmed (see new ILAE definition above).

The initial evaluation of patients suspected of having epilepsy should lead to the suspicion/confirmation of the diagnosis, its type and in some situations, its etiology (in the case of focal/partial epilepsy). As defined by the ILAE subcommission on AED guidelines, the ultimate judgment for therapy must be made in light of all the clinical data presented by the patient and by the treatment options that are locally available for the patient and his/her clinician [47]. Another principle is using drugs that are appropriate to the patient's seizure type(s), as focal and generalized epilepsies can demonstrate responsiveness to, and at times aggravation from individual drugs or classes of drugs.

Pharmacokinetics and pharmacodynamics of AEDs should be especially considered in elderly patients because of frequent comorbidities that can alter drug metab-

Table 18.3 Who should be treated after the first seizure?

The initiation of medical treatment is recommended after the first seizure if one of the following details is present
<ul style="list-style-type: none"> • Complex partial seizure (e.g., seizures with described focal features that may include aura; focal motor, sensory and/or visual features; the presence of oral or manual automatisms) • When the first presenting seizure had actually been preceded by previously undiagnosed seizure manifestations such as absences, myoclonus or auras • Abnormal neurological examination • Abnormal EEG: in particular, studies showing epileptic abnormalities (spikes, sharp waves that usually point to at least an increased susceptibility of the brain or part of it for the generation of epileptic seizures) • Abnormal MRI: in particular, studies showing cortical-based lesions, sequelae of ischemic hemorrhagic events or hippocampal abnormalities
Treatment may also be considered after a first seizure even in the absence of the above risk factors if there was severe injury or consequences from the first seizure

olisms and drug-drug interactions due to concomitant chronic treatment for other pre-existing conditions. Compliance usually depends on absence of side effects and number of prescribed medications [48]. Careful review of appropriateness of all prescribed medications through a multidisciplinary approach should be especially considered for this age group. Whenever possible important to avoid medications which can lower seizure threshold (for example, bupropion, tramadol, olanzapine).

Pharmacokinetic-pharmacodynamic interactions are changing with age. The most prominent is the decrease in the excretory capacity of the kidneys. On the other hand, a change in sensitivity to medications is also commonly described in elderly patients. However, central nervous system medications (such as benzodiazepines) become more potent and should be used cautiously [49]. The general rule “start low and go slow” is especially important for elderly patients. Hepatic drug metabolism varies to a lesser extent with age [50], however medications such as liver enzyme inducers can markedly alter the metabolism of some antiepileptic drugs (AED). Conversely, AEDs that influence hepatic metabolism can change blood levels of concomitant medications.

The Choice of the First Antiepileptic Medication

Lamotrigine (LTG), levetiracetam (LEV), gabapentin (GBP), carbamazepine (CBZ) are the most investigated antiepileptic medications in elderly population. In general, studies failed to show difference in efficacy among AED (reported rate of seizure freedom was 50–70%), however, highlighted significantly different rate of side effects.

LTG and [51, 52] as well as LEV [53] was studied in several double blind randomized-controlled trials and demonstrated better tolerability compared to CBZ.

The efficacy of Topiramate (TPM) in elderly patients was similar between low-dose and high-dose group, however, two thirds of patients experienced adverse reactions such as somnolence, dizziness, headache or cognitive side effects [48].

Oxcarbazepine (OXC) monotherapy in elderly patients was associated with seizure freedom in 73% of patients and discontinuation of OXC due to side effects in 9% [54].

Overall, the current tendency is to use or move to newer antiepileptic medications such as LEV and LTG as first line treatments in elderly patients [55].

LTG and LEV are the most studied medications in patients with AD. These AED were better tolerated compared to phenobarbital (PB), however, seizure control rate was similar. Patients treated with PB had more cognitive side effects, while the LEV group showed better attention and oral fluency performance, and the LTG group reported better mood [24, 26]. The following options should be considered for initial monotherapy for elderly adults with newly diagnosed or untreated partial onset seizures: (1) GBP, LTG and LEV (Level A evidence), (2) CBZ (Level B evidence), and (3) TPM and valproic acid (VPA) (Level D evidence). Figure 18.1 illustrates a carepath for the diagnosis and treatment of epilepsy.

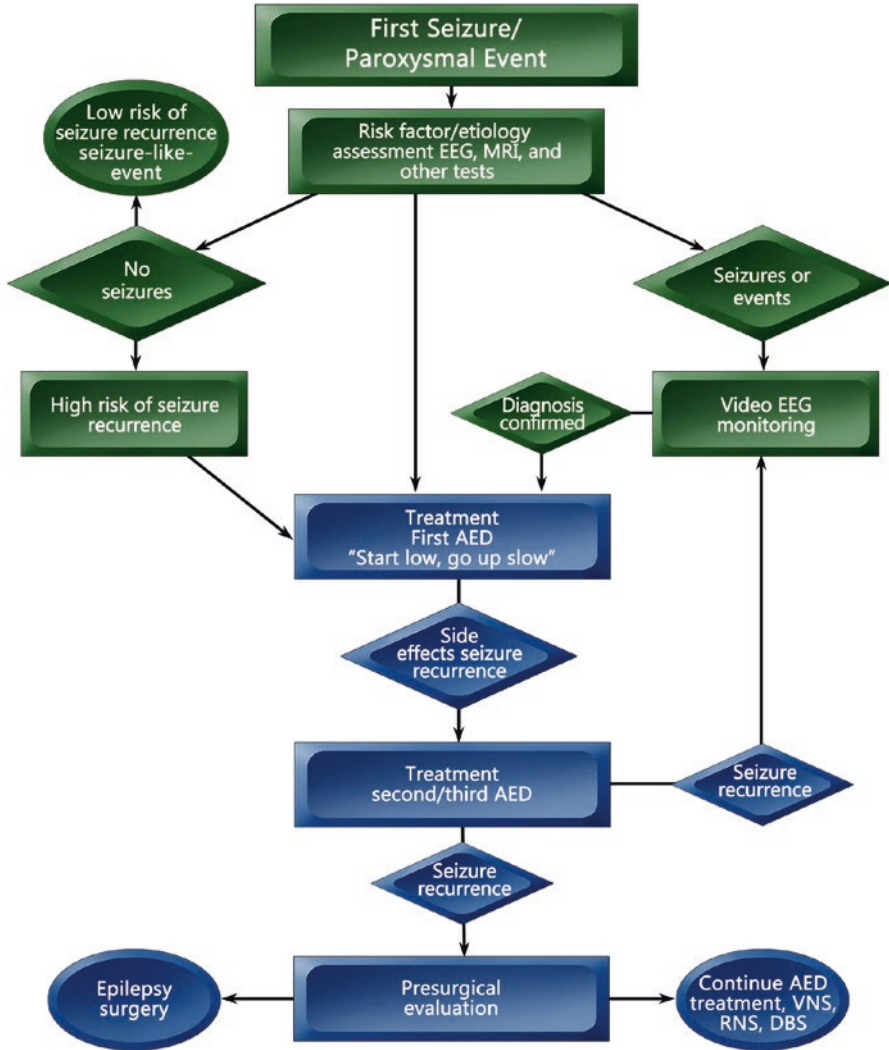


Fig. 18.1 Diagnosis and treatment of epilepsy

For oral LTG starting dose is 25 mg per day (one or two divided doses). Dose should be increased in 2 week by 25 mg and after fifth week by 50 mg per day every 1–2 weeks. Maintain dose is from 200 to 400 mg per day divided in two doses.

In patients taking VPA initial dose of LTG should be 25 mg every other day first 2 weeks and 25 mg every day during week 4 and 5.

Starting dose for oral LEV is 1000 mg a day (two divided doses). The dose can be increased by 1000 mg every 2 weeks. The maximal dose is 3000 mg a day.

Side Effects Monitoring

Idiosyncratic skin reactions are more common in elderly patients and in some cases can be life threatening (for example Stevens-Johnson's syndrome). Phenobarbital, phenytoin, carbamazepine, lamotrigine and zonisamide treatment are more frequently associated with skin rash [56]. History of previous allergic reaction can be the reason to avoid medications that can produce skin rash [50].

Antiepileptic medications can alter Vitamin D metabolism and increase risk of osteoporosis. Long term use of any antiepileptic medication (enzyme inducers and non-enzyme inducers) increases risk of fractures, especially in women with epilepsy [57]. Bone mineral density measures 1 year after AED (LEV, CBZ or valproic acid (VPA)) treatment initiation is showing clinically relevant reduction in bone turnover [58].

Liver enzyme-inducing antiepileptic medications such as phenobarbital, phenytoin, and carbamazepine can increase serum sex hormone-binding globulin concentrations and diminish bioactive testosterone and estradiol. Whereas valproic acid can increase serum testosterone and free androgen index [59].

Patients receiving CBZ or VPA has ninefold increase risk of aplastic anemia [60].

Clinically significant ($\text{Na}^+ \leq 128 \text{ mEq/L}$) hyponatremia was observed in 12.4% of patients receiving OXZ treatment and 2.8% of those receiving CBZ treatment [61]. Risk of hyponatremia increases with patient age and in patients on polypharmacotherapy [62]. The symptoms usually are headache, general malaise, gait disturbance, and somnolence.

The following recommendations could be made for management of elderly patients with epilepsy:

1. Cognitive decline/dementia: influence on treatment adherence and self-report about the seizures. Consider cognitive screening, supervise medication intake, provide care training.
2. Psychiatric comorbidities: decrease quality of life and influence on treatment adherence. Consider routine screening for depression and anxiety disorders.
3. Stroke (cerebrovascular disease): common risk factors for epilepsy and cerebrovascular diseases. Consider its assessment and preventive management.
4. Osteoporosis. AED can increase risk of bone loss. Consider Calcium and Vitamin D supplementation.
5. Chronic renal disease alters elimination of some AED: Consider dose adjustment and change in the AED.

Surgical Treatment of Epilepsy

One-third of patients with epilepsy may have difficult-to-control seizures affecting both the patient's and his/her family's quality of life. Surgical evaluation is recommended when two or more appropriately chosen and used antiepileptic medications failed to completely control a patient's seizures [63].

Pharmacoresistance

Failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic medications.

Current literature suggest that outcome of epilepsy surgery in elderly as well as rate of complications is not different compare to younger adults [64, 65]. Complete seizure freedom can be achieved in 50–70% of patients and significant seizure reduction in up to 90% of patients [66, 67].

Presurgical evaluation (and epilepsy surgery) should be performed only at Comprehensive Epilepsy Centers (National Association of Epilepsy Centers, NAEC) as it requires a highly subspecialized multidisciplinary team approach, clinical expertise and experience that are complemented by validated outcomes on a large number of patients.

Steps for Candidate Selection and Presurgical Evaluation

- Confirm the diagnosis of epilepsy
- Establish the medical intractability of the epilepsy (pharmacoresistance)
- Establish the presence of focal epilepsy (single epileptic region)
- Identify a possible cause for the focal epilepsy (focal pathology)
- Assess the function of the epileptic region

ICD 10 Codes

Epilepsy and Recurrent Seizures G40-

- the following terms are to be considered equivalent to intractable: pharmacoresistant (pharmacologically resistant), treatment resistant, refractory (medically) and poorly controlled

Type 1 Excludes

- conversion disorder with seizures (F44.5)
- convulsions NOS (R56.9)
- post traumatic seizures (R56.1)
- seizure (convulsive) NOS (R56.9)
- seizure of newborn (P90)

Type 2 Excludes

- hippocampal sclerosis (G93.81)
- mesial temporal sclerosis (G93.81)
- temporal sclerosis (G93.81)
- Todd's paralysis (G83.84)

Clinical Information

- A brain disorder characterized by episodes of abnormally increased neuronal discharge resulting in transient episodes of sensory or motor neurological dysfunction, or psychic dysfunction. These episodes may or may not be associated with loss of consciousness or convulsions.
- A disorder characterized by recurrent episodes of paroxysmal brain dysfunction due to a sudden, disorderly, and excessive neuronal discharge. Epilepsy classification systems are generally based upon: (1) clinical features of the seizure episodes (e.g., motor seizure), (2) etiology (e.g., post-traumatic), (3) anatomic site of seizure origin (e.g., frontal lobe seizure), (4) tendency to spread to other structures in the brain, and (5) temporal patterns (e.g., nocturnal epilepsy). (from Adams et al., Principles of Neurology, 6th ed., p. 313)
- A disorder characterized by recurrent seizures
- A group of disorders marked by problems in the normal functioning of the brain. These problems can produce seizures, unusual body movements, a loss of consciousness or changes in consciousness, as well as mental problems or problems with the senses.
- Brain disorder characterized by recurring excessive neuronal discharge, exhibited by transient episodes of motor, sensory, or psychic dysfunction, with or without unconsciousness or convulsive movements.
- Epilepsy is a brain disorder that causes people to have recurring seizures. The seizures happen when clusters of nerve cells, or neurons, in the brain send out the wrong signals. People may have strange sensations and emotions or behave strangely. They may have violent muscle spasms or lose consciousness. Epilepsy has many possible causes, including illness, brain injury and abnormal brain development. In many cases, the cause is unknown doctors use brain scans and other tests to diagnose epilepsy. It is important to start treatment right away. There is no cure for epilepsy, but medicines can control seizures for most people. When medicines are not working well, surgery or implanted devices such as vagus nerve stimulators may help. Special diets can help some children with epilepsy.

G40 Epilepsy and recurrent seizures

G40.0 Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset

G40.00 Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable

G40.001 ... with status epilepticus

G40.009 ... without status epilepticus

- G40.01 Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, intractable
 - G40.011 ... with status epilepticus
 - G40.019 ... without status epilepticus
- G40.1 Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures
 - G40.10 Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable
 - G40.101 ... with status epilepticus
 - G40.109 ... without status epilepticus
 - G40.11 Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable
 - G40.111 ... with status epilepticus
 - G40.119 ... without status epilepticus
- G40.2 Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures
 - G40.20 Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable
 - G40.201 ... with status epilepticus
 - G40.209 ... without status epilepticus
 - G40.21 Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable
 - G40.211 ... with status epilepticus
 - G40.219 ... without status epilepticus
- G40.3 Generalized idiopathic epilepsy and epileptic syndromes
 - G40.30 Generalized idiopathic epilepsy and epileptic syndromes, not intractable
 - G40.301 ... with status epilepticus
 - G40.309 ... without status epilepticus
 - G40.31 Generalized idiopathic epilepsy and epileptic syndromes, intractable
 - G40.311 ... with status epilepticus
 - G40.319 ... without status epilepticus

G40.A Absence epileptic syndrome**G40.A0** Absence epileptic syndrome, not intractable**G40.A01** ... with status epilepticus**G40.A09** ... without status epilepticus**G40.A1** Absence epileptic syndrome, intractable**G40.A11** ... with status epilepticus**G40.A19** ... without status epilepticus**G40.B** Juvenile myoclonic epilepsy [impulsive petit mal]**G40.B0** Juvenile myoclonic epilepsy, not intractable**G40.B01** ... with status epilepticus**G40.B09** ... without status epilepticus**G40.B1** Juvenile myoclonic epilepsy, intractable**G40.B11** ... with status epilepticus**G40.B19** ... without status epilepticus**G40.4** Other generalized epilepsy and epileptic syndromes**G40.40** Other generalized epilepsy and epileptic syndromes, not intractable**G40.401** ... with status epilepticus**G40.409** ... without status epilepticus**G40.41** Other generalized epilepsy and epileptic syndromes, intractable**G40.411** ... with status epilepticus**G40.419** ... without status epilepticus**G40.5** Epileptic seizures related to external causes**G40.50** Epileptic seizures related to external causes, not intractable**G40.501** ... with status epilepticus**G40.509** ... without status epilepticus**G40.8** Other epilepsy and recurrent seizures**G40.80** Other epilepsy**G40.801** ... not intractable, with status epilepticus**G40.802** ... not intractable, without status epilepticus**G40.803** ... intractable, with status epilepticus**G40.804** ... intractable, without status epilepticus

G40.81 Lennox-Gastaut syndrome

G40.811 ... not intractable, with status epilepticus

G40.812 ... not intractable, without status epilepticus

G40.813 ... intractable, with status epilepticus

G40.814 ... intractable, without status epilepticus

G40.82 Epileptic spasms

G40.821 ... not intractable, with status epilepticus

G40.822 ... not intractable, without status epilepticus

G40.823 ... intractable, with status epilepticus

G40.824 ... intractable, without status epilepticus

G40.89 Other seizures**G40.9** Epilepsy, unspecified**G40.90** Epilepsy, unspecified, not intractable

G40.901 ... with status epilepticus

G40.909 ... without status epilepticus

G40.91 Epilepsy, unspecified, intractable

G40.911 ... with status epilepticus

G40.919 ... without status epilepticus

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Chapter 19

Sleep Disorders

Carlos L. Rodriguez and Nancy Foldvary-Schaefer

Clinical Pearls

- Cognitive Behavior Therapy for Insomnia (CBT-I) has been shown to be an effective treatment for primary insomnias as well as comorbid insomnias. Sleep hygiene measures in isolation are typically not effective.
- Obstructive Sleep Apnea (OSA) in the elderly can be more challenging to diagnose because these patients are less likely to report snoring and witnessed apneas and they are usually thinner than younger adult OSA patients.
- Providers must specifically ask patients whether they have symptoms suggestive of REM Sleep Behavior Disorder (RBD), as most patients will not spontaneously volunteer this history. The diagnosis requires polysomnography (PSG) with upper extremity electromyographic (EMG) monitoring. A standard PSG with the typical montage employed for the evaluation of sleep disordered breathing can miss the diagnosis.

Introduction

Elderly individuals are at increased risk for sleep disturbances due to a variety of factors including comorbid medical and psychiatric disorders, social stressors, polypharmacy, and physiological changes that accompany aging. However, contrary to popular belief, sleep disturbances should not be assumed to be an inherent part of the aging process. Many elderly adults needlessly suffer from treatable conditions. Sleep disorders represent an opportunity to prevent the development or progression of medical and psychiatric disorders, reduce morbidity and even mortality, and improve quality of life (QOL),

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mood, and cognition. Herein, we review the diagnosis and treatment of the most common sleep disorders and those with particular implications in elderly populations.

Sleep and Normal Aging

The normal aging process is associated with changes in sleep quality and quantity as well as alterations in circadian rhythms that affect the timing of sleep [1, 2]. Older individuals experience an advance in sleep to earlier hours that can adversely affect social and psychiatric functioning. Sleep is characterized by reduced sleep efficiency, increased number of awakenings, and reduced slow wave sleep leading to dissatisfaction with sleep quality for many. Daytime sleepiness and fatigue are commonly reported and napping increases. The National Sleep Foundation's 2015 sufficient sleep duration requirements recommended 7–8 h of sleep for older, healthy adults [3]. The 2004 National Sleep Foundation survey found that sleep complaints common in older adults were typically secondary to medical comorbidities, depression, and pain and not to aging per se [4]. Therefore, normal age-related changes in sleep must be distinguished from pathological conditions. This differentiation requires a detailed sleep, medical and psychiatric history, caregiver observations, and review of medications including over-the-counter agents, alcohol, and tobacco use, as well as lifestyle habits. Sleep logs and laboratory testing may be required depending on the nature of the complaint.

Classification of Sleep Disorders

The *International Classification of Sleep Disorders, Third Edition (ICSD-3)* published by the American Academy of Sleep Medicine [5] categorizes the following six groups of sleep disorders:

- Insomnias
- Sleep related breathing disorders
- Central disorders of hypersomnolence
- Circadian rhythm sleep-wake disorders
- Parasomnias
- Sleep related movement disorders

Insomnias

Insomnia is defined as a persistent difficulty with sleep initiation, duration, consolidation, or quality despite an adequate opportunity and circumstance for sleep, which results in daytime impairment [5]. Historically, insomnia was subdivided into primary insomnia (in which no other cause was present) and secondary insomnia (due to a medical, psychiatric, or other sleep disorder). Secondary insomnias often

develop an independent course from the underlying etiology and can persist following its resolution. In fact, secondary insomnia may itself have effects on the underlying cause of the insomnia as in the classic example of insomnia and comorbid depression. This has led to the recognition that secondary insomnias should be regarded as comorbid disorders in which there are bidirectional or interactive effects between the insomnia and the underlying cause. As such, the term comorbid insomnia is used rather than secondary insomnia.

Insomnia is the most common sleep problem, with approximately 30–40% of adults reporting some degree of insomnia symptoms within any given year, and 10–15% affected by insomnia disorders [6–8]. In addition to older age, risk factors include depression, lower socioeconomic status, medical and psychiatric comorbidities, female gender, African American (vs. Caucasian) race, and divorce/separation (vs. married or never married individuals) [9]. In patients greater than 65 years of age, polypharmacy, medical comorbidities, and comorbid sleep disorders contribute to higher frequencies of insomnia disorders. Insomnia is associated with a host of adverse outcomes including depression, substance abuse, hypertension, heart disease, metabolic syndrome, pain, cognitive impairment as well as absenteeism, reduced productivity, and increased healthcare utilization [8]. It should be noted that the majority of adults experience insomnia symptoms at some point in life that do not affect daytime functioning, and therefore, do not meet diagnostic criteria.

There are two forms of insomnia disorders (chronic insomnia disorder and short-term insomnia disorder) which are distinguished primarily by duration and apply to patients with and without comorbidities regardless of whether the comorbidities are sleep disruptive.

Chronic Insomnia Disorder

Diagnostic criteria for chronic insomnia disorder are shown in Table 19.1. Individuals with chronic insomnia disorders can demonstrate a pattern of conditioned arousal characterized by falling asleep easily in settings outside the bedroom when not trying to sleep, but exhibit cognitive and somatic arousal when actively attempting to fall asleep in bed. Inadequate sleep hygiene is commonly observed, consisting of habitual activities which are not conducive with good sleep such as clock watching, rumination, and fear of the consequences of sleep loss. Some display a marked propensity to underestimate the amount of sleep they actually obtain.

The diagnosis of insomnia disorders is established by a detailed sleep, medical, and psychiatric history (Table 19.2) and review of current medications and substance use that may be contributing to the sleep disturbance (Table 19.3).

Sleep diaries and actigraphy are helpful in characterizing sleep patterns, excluding circadian rhythm disorders, and tracking treatment response. Polysomnography (PSG) is not indicated solely for the evaluation of insomnia. However, testing should be considered when comorbid sleep apnea or dream enacting behaviors (DEBs) concerning for REM sleep behavior disorder (RBD) is suspected.

The differential diagnosis of chronic insomnia includes circadian rhythm disorders, such as delayed sleep-wake phase disorder and irregular sleep-wake rhythm disorder, environmental factors such as light and sound that interfere with sleep,

Table 19.1 Diagnostic criteria for chronic insomnia disorder

Criteria 1–6 must be met:
1. The patient/caregiver reports one or more of the following;
a. Difficulty initiating sleep
b. Difficulty maintaining sleep
c. Waking up earlier than desired
d. Resistance to going to bed on appropriate schedule
e. Difficulty sleeping without caregiver intervention
2. The patient/caregiver reports one or more of the following related to the night sleep disturbance:
a. Fatigue/daytime sleepiness
b. Attention, concentration or memory impairment
c. Impaired social, occupational or academic performance
d. Mood disturbance/irritability
e. Behavioral problems
f. Reduced motivation or energy
g. Proneness for errors or accidents
h. Sleep dissatisfaction
3. Symptoms cannot be explained solely by inadequate opportunity for sleep
4. Symptoms occur at least three times per week
5. Symptoms have been present for at least 3 months
6. Symptoms are not better explained by another sleep disorder

Adapted from ICSD-3, 2014

Table 19.2 Comorbid conditions associated with insomnia

• Neurological: dementias, Parkinson's disease, headache disorders, traumatic brain injury, epilepsy, neuromuscular disorders, stroke
• Cardiovascular: heart failure, angina, dyspnea, arrhythmias
• Pulmonary: chronic obstructive lung disease, asthma
• Digestive: gastro-esophageal reflux disease, peptic ulcer disease, irritable bowel syndrome
• Genitourinary: incontinence, benign prostatic hypertrophy, nocturia, interstitial cystitis, chronic kidney disease
• Endocrine: hypothyroidism, hyperthyroidism, diabetes mellitus, menopause
• Musculoskeletal: rheumatoid arthritis, osteoarthritis, fibromyalgia, Sjogren's syndrome
• Psychiatric: mood disorders, anxiety disorders, psychotic spectrum disorders
• Other: chronic pain, cancer

insufficient sleep syndrome defined by volitional sleep restriction, psychiatric disorders including depression, and restless legs syndrome (RLS). Validated subjective instruments serve as useful adjuncts to the sleep history in the evaluation of insomnia complaints and other sleep presentations. These include the Insomnia Severity Index (ISI) [10], Fatigue Severity Scale (FSS) [11], Epworth Sleepiness Scale (ESS) [12], Patient Health Questionnaire-9 (PHQ-9) for depression [13], International Restless Legs Syndrome Study Group Rating Scale (IRLSSG) [14], and the STOP-BANG for obstructive sleep apnea (OSA) [15].

Table 19.3 Medications and substances associated with insomnia

- | |
|--|
| • Antidepressants: selective serotonin reuptake inhibitors, selective serotonin norepinephrine reuptake inhibitors, monoamine oxidase inhibitors |
| • Cardiovascular: beta-blockers, alpha-receptor agonists and antagonists, diuretics, lipid lowering agents |
| • Decongestants: pseudoephedrine, phenylephrine, phenylpropanolamine |
| • Endocrine: glucocorticoids, levothyroxine, leuprolide |
| • Opioids: Oxycodone, codeine, propoxyphene |
| • Stimulants/wake promoting agents: methylphenidate, amphetamine derivatives, ephedrine derivatives, caffeine, modafinil, armodafinil |
| • Respiratory: theophylline, albuterol |
| • Substances: alcohol, nicotine, cocaine |

Table 19.4 Diagnostic criteria for short-term insomnia disorder

- | |
|---|
| Criteria 1–5 must be met: |
| 1. The patient/caregiver reports one or more of the following; |
| a. Difficulty initiating sleep |
| b. Difficulty maintaining sleep |
| c. Waking up earlier than desired |
| d. Resistance to going to bed on appropriate schedule |
| e. Difficulty sleeping without caregiver intervention |
| 2. The patient/caregiver reports one or more of the following related to the night sleep disturbance: |
| a. Fatigue/daytime sleepiness |
| b. Attention, concentration or memory impairment |
| c. Impaired social, occupational or academic performance |
| d. Mood disturbance/irritability |
| e. Behavioral problems |
| f. Reduced motivation or energy |
| g. Proneness for errors or accidents |
| h. Sleep dissatisfaction |
| 3. Symptoms cannot be explained solely by inadequate opportunity for sleep |
| 4. Symptoms occur at least three times per week |
| 5. Symptoms have been present for less than 3 months |
| 6. Symptoms are not better explained by another sleep disorder |

Adapted from ICSD-3, 2014

Short-Term Insomnia Disorder

Diagnostic criteria are shown in Table 19.4. Short-term insomnia is typically preceded by an acute, identifiable cause that triggers the sleep disturbance. Common examples include bereavement, job loss, divorce, comorbid conditions, hospitalization, and abrupt changes in daily routines in the elderly.

Table 19.5 Sleep hygiene tips

-
- Go to bed at a regular time and avoid napping late in the afternoon. Limit naps to 10–15 min no later than late afternoon

 - Get aerobic exercise during the day but avoid anything too strenuous within 3 h of bedtime

 - Avoid eating within 2 h of bedtime

 - Stop working at any task an hour before bedtime

 - Minimize noise with earplugs and minimize light with window blinds, curtains, or eye masks

 - At bedtime, avoid worrying or planning. Learn a relaxation technique and practice it in bed

 - Keep pets outside of the bedroom

 - Make sure the bedroom is well-ventilated and at a comfortable temperature (below 75 °F)

 - Use the bedroom for sleep and intimate relations only. If unable to fall asleep within 20 min, go into another room and read or watch television until feeling sleepy

 - Avoid caffeine at least 4–6 h before bedtime

 - Avoid alcohol and nicotine near bedtime and during the night

Treatment of Insomnia Disorders

Interventions for insomnia disorders include cognitive behavioral therapy for insomnia (CBT-I), symptomatic pharmacotherapy, treatment of comorbid conditions contributing to the sleep complaint, and removal of inciting factors such as caffeine, alcohol, and nicotine. Sleep hygiene tips are shown in Table 19.5.

CBT-I is the treatment of choice in the majority of patients with chronic insomnia disorders. CBT-I is a multifaceted treatment approach that tailors a combination of strategies (stimulus control therapy, sleep hygiene, sleep restriction, cognitive therapy, paradoxical intention, and relaxation therapy) individualized for each patient. Efficacy of this approach compared with pharmacotherapy alone or placebo has been demonstrated in patients of all ages including the elderly [8, 16]. Significant improvements are achieved in up to 70% of patients with both primary and comorbid insomnia [17].

CBT-I is typically provided by a psychologist or therapist with expertise in behavioral treatments for sleep disorders. Skill development often takes several weeks, so the benefits are more delayed than from taking a sleep medication, but CBT-I avoids long-term use of sleep medications whose side effects can be problematic in the elderly. Successful treatment requires that the patient and/or caregiver accept, understand, and consistently implement the treatment plan. Treatment typically takes place over the course of 4–8 individual sessions with a therapist, but group and web-based delivery methods are also effective. Failure to achieve a good response within 3–4 months should prompt the clinician to explore adherence and assess for other unrecognized or sub optimally controlled comorbid medical or sleep disorders.

Drugs approved by the FDA for the treatment of insomnia include barbiturates, benzodiazepine receptor agonists (benzodiazepines and non-benzodiazepines), antihistamines, the tricyclic drug doxepin, the melatonin receptor agonist ramelteon, and the orexin receptor antagonist drug suvorexant [18]. Sedating antidepressants, antipsychotics and anticonvulsants are also commonly prescribed off-label for insomnia.

Barbiturates and benzodiazepines have been replaced by the non-benzodiazepine receptor agonists and other agents due to their potential for toxicity. The non-benzodiazepine receptor agonist agents are effective in shortening sleep latency and reducing arousals and awakenings. Adverse effects include morning sedation, cognitive impairment, and gait disturbance that can lead to falls and hip fractures in the elderly. A meta-analysis of hypnotic trials in older adults found adverse cognitive events 4.78 times more common, psychomotor events 2.61 times more common, and fatigue 3.82 times more common in those using any hypnotic compared with placebo [19]. The elderly are particularly vulnerable due to increased polypharmacy, age-related decreases in drug metabolism and clearance, and comorbid medical and psychiatric disorders. As individuals become increasingly physically and cognitively frail, the risks of pharmacotherapy begin to outweigh their benefits.

In 2007, the FDA issued a black box warning for prescription hypnotics due to the potential for complex sleep related behaviors including sleep eating, sleep walking, sleep driving, and sexual behaviors during sleep. Subsequently, the FDA required the manufacturers of eszopiclone and zolpidem to decrease the recommended dose of zolpidem immediate-release from 10 to 5 mg and extended-release from 12.5 to 6.25 mg in women and eszopiclone from 3 to 1 mg in both genders, due to data demonstrating morning blood levels high enough in some to impair activities that require alertness, including driving. The most important considerations in hypnotic selection in the elderly include the temporal pattern of insomnia (sleep initiation vs. sleep maintenance difficulty) and drug pharmacokinetics. In general, the lowest effective dose is recommended. Commonly prescribed prescription hypnotics are shown in Table 19.6.

Table 19.6 FDA-approved medications for insomnia

Drug	Indication	Usual adult dose (mg)	T1/2 (h)	Active metabolites
<i>Benzodiazepines</i>				
Estazolam (ProSom)	Maintenance	0.5–2.0	8–24	No
Flurazepam (Dalmane)	Maintenance	15–30	2–5 ^a	Yes
Quazepam (Doral)	Maintenance	7.5–30	47–120 ^b	Yes
			15–40 ^a	
Temazepam (Restoril)	Maintenance	7.5–30	39–120 ^b	No
Triazolam (Halcion)	Onset	0.125–0.25	8–20	No
			1.5–5	
<i>Benzodiazepine receptor agonists</i>				
Eszopiclone (Lunesta)	Onset, Maintenance	1–3	6.0	No
Zaleplon (Sonata)	Onset, Maintenance	5–10	1.0	No
Zolpidem (Ambien)	Onset	5–10	1.5–4.5	No
Zolpidem CR (Ambien CR)	Onset, Maintenance	6.25–12.5	1.6–4.0	No
		1.75–3.5		No

(continued)

Table 19.6 (continued)

Drug	Indication	Usual adult dose (mg)	T1/2 (h)	Active metabolites
Zolpidem sublingual	Maintenance	1.75mg once per night only if ≥ 4 h remain before waking up		
<i>Melatonin receptor agonist</i>				
Ramelteon (Rozerem)	Onset	8	1–2.6 ^a	Yes
			2–5 ^b	
<i>Tricyclic antidepressant</i>				
Doxepin (Silenor)	Maintenance	3–6	15.3 ^a	Yes
			31.0 ^b	
<i>Orexin receptor antagonist</i>				
Suvorexant (Belsomra)	Onset, maintenance	10–20	12	No

^aParent compound^bActive metabolite

CBT-I Versus Pharmacotherapy

Figure 19.1 illustrates an algorithm for the treatment of insomnia. When deliberating between CBT-I and pharmacotherapy for insomnia, the following general guidelines should be applied.

- CBT-I is recommended for the treatment of chronic insomnia disorder as an initial intervention whenever possible, given its superior effectiveness as compared to pharmacotherapy in both younger and older adults over periods up to 3 years [16, 17]. CBT-I combined with pharmacotherapy has not been systematically shown to be superior to CBT-I alone [6].
- Either CBT-I or pharmacotherapy may be considered as initial treatment for short-term insomnia. Following transient life stressors, or other cases in which patient motivation, preference, finances, or insurance coverage may not align with CBT-I, the non-benzodiazepine receptor agonists are common initial considerations. Short-term medication trials in these situations may prevent escalation of symptoms leading to a chronic insomnia disorder.
- When starting a hypnotic medication, the expected duration of treatment should be discussed and discontinuation at some fixed point in time should be determined [18].
- Long-term hypnotic use may be appropriate in rare cases of refractory insomnia, those who have not responded to CBT-I or short-term pharmacotherapy, and in patients with chronic comorbid illness [20].

It is important to optimize treatment of comorbid medical and psychiatric conditions that may be contributing to insomnia complaints. In some situations, pharmacotherapy, generally off-label, can be targeted to address multiple com-

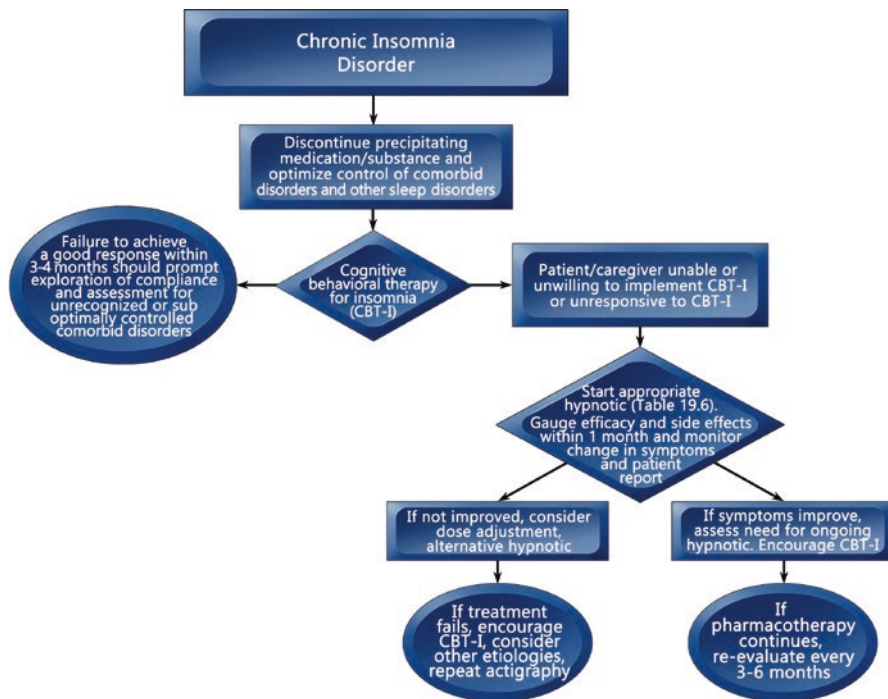


Fig. 19.1 Treatment of insomnia

plaints. In patients with depression or anxiety, mirtazapine at bedtime or selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors (SSRIs/SNRIs) in the morning may address both depressive and insomnia symptoms. Similarly, gabapentin or pregabalin may be considered in patients with insomnia and restless legs syndrome, anxiety, or pain. When insomnia symptoms present after initiation of a medication or substance, the inciting agent should be discontinued.

Sleep Related Breathing Disorders

Sleep related breathing disorders (SRBD) are characterized by abnormalities of respiration during sleep that include OSA, central sleep apnea, sleep related hypoventilation disorders, and sleep related hypoxemia disorder [5]. OSA is the most common sleep related breathing disorder in all ages. Central sleep apnea (CSA), sleep related hypoventilation, and sleep related hypoxemia may increase with age due to cardiopulmonary and neurologic comorbidities.

Obstructive Sleep Apnea

OSA is characterized by repetitive episodes of partial (hypopnea) or complete (apnea) obstruction of the upper airway during sleep. Epidemiological studies indicate that 24% of men and 9% of women have OSA defined as an apnea-hypopnea index (AHI) of ≥ 5 on PSG, although only 4% of men and 2% of women have daytime sleepiness [21]. The prevalence of OSA increases with age peaking at around 60 years [22], such that the odd ratio for AHI increases by 1.79 (95% CI: 1.41–2.27) per 10-year increment [23]. The gender disparity observed in middle-aged adults favoring males diminishes with age, rendering females 50 years of age and older comparably at risk as their age-matched male counterparts [23]. This change has been largely attributed to the loss of protective female sex hormones associated with menopause. It has been estimated that up to 80% of OSA is undiagnosed [24], illustrating its significant public health implications given the association of moderate-to-severe OSA with hypertension, cardiovascular disease, hyperlipidemia, stroke, glucose intolerance, depression, motor vehicle or occupational accidents, increased healthcare utilization, and cardiovascular mortality [25].

Diagnostic criteria for OSA are shown in Table 19.7. The clinical manifestations of OSA in the elderly often differ from those of younger adults. Witnessed apnea, snoring, obesity and increased neck circumference are significantly less predictive of moderate-to-severe OSA in older versus younger adults [22]. Chronic comorbidities can lead to fatigue and excessive daytime sleepiness (EDS) such that patients and caregivers fail to attribute daytime symptoms to a sleep disorder.

The evaluation of sleep related breathing disorders begins with a sleep, medical, and psychiatric history, review of medications and substances that affect sleep and

Table 19.7 Diagnostic criteria for obstructive sleep apnea

Criteria 1 and 2 or 3 must be met:
1. The presence of one or more of the following:
a. Excessive sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms
b. Waking with breath holding, gasping, or choking
c. Observer reports of snoring, breathing interruptions or both during sleep
d. Diagnosis of hypertension, coronary artery disease, stroke, heart failure, atrial fibrillation, type 2 diabetes mellitus, mood disorder, or cognitive impairment
2. PSG or HSAT demonstrates:
a. Five or more predominantly obstructive respiratory events per hour of sleep (PSG) or per hour of monitoring (HSAT)
OR
3. PSG or HSAT demonstrates:
a. Fifteen or more predominantly obstructive respiratory events per hour of sleep (PSG) or per hour of monitoring (HSAT)

Adapted from ICSD-3, 2014

PSG polysomnography, HSAT home sleep apnea testing

Table 19.8 Physical examination findings in obstructive sleep apnea

• Body mass index >30 kg/m ²
• Neck circumference > 17 inches in men and >16 inches in woman
• Nasal obstruction (turbinate hypertrophy, septal deviation, polyps)
• Nasal valve incompetence
• Mandibular retrognathia
• Macroglossia
• Scalloping along lateral tongue
• Small oral cavity (overlapping teeth)
• Low-hanging and elongated soft palate
• Large, elongated or swollen uvula
• Overjet
• Tonsillar hypertrophy
• Oropharyngeal crowding
• High arched or narrow palate

wakefulness, and physical examination focusing on the head and neck (Table 19.8). Medications associated with EDS include hypnotics, antidepressants, antipsychotics, sedating antihistamines, valerian, melatonin, dopamine agonists, opioids, anticonvulsants, anticholinergics, antispasmodics, antiemetics, antiarrhythmics, nonsteroidal anti-inflammatory drugs, beta-blockers, some antibiotics, alcohol, and marijuana. Alternative diagnostic considerations in patients presenting with nocturnal gasping or dyspnea including paroxysmal nocturnal dyspnea, nocturnal angina, nocturnal panic attacks, gastro-esophageal reflux, and asthma should be excluded.

In-laboratory PSG is required for the diagnosis of the sleep related breathing disorders. Home sleep apnea testing (HSAT) is preferred to confirm the diagnosis in those with high pre-test probability for moderate-to-severe disease OSA but is specifically discouraged in patients over 65 years of age [26]. Devices used in the home generally do not record parameters needed to stage sleep or identify sleep-related motor activity, thereby underestimating OSA severity. HSAT is inadequate in the setting of medical comorbidities including heart failure, moderate-to-severe cardiac and/or pulmonary disease, and neuromuscular disorders and is also contraindicated in the presence of comorbid sleep disorders such as insomnia, circadian rhythm disorders, parasomnias, and narcolepsy [26]. The STOP-BANG questionnaire, widely used to identify patients with high OSA pre-test probability, has a sensitivity of nearly 93% for moderate-to-severe disease [15].

Other Sleep Related Breathing Disorders

Central sleep apnea disorders are classified as idiopathic or related to high altitude, opioids, CNS lesions (brainstem or bilateral hemispheric) or due to Cheyne-Stokes breathing pattern (CSR). Central sleep apnea is characterized by a lack of drive to

breathe during sleep, resulting in repetitive periods of insufficient ventilation and compromised oxygen supply. Central sleep apnea with Cheyne-Stokes breathing pattern, consisting of periods of hyperventilation in association with waxing and waning tidal volume alternating with central apneas, is highly prevalent in chronic heart failure patients. Sleep related hypoventilation is characterized by insufficient ventilation resulting in abnormally elevated arterial partial pressure of carbon dioxide during sleep and is most commonly seen in the setting of morbid obesity. Patients may meet diagnostic criteria for more than one of these groups.

Treatment of Sleep Related Breathing Disorders

Continuous Positive Airway Pressure (CPAP) is the treatment of choice for patients with moderate-to-severe OSA. A 2009 meta-analysis concluded that CPAP is a medically effective and cost-effective treatment compared with placebo and conservative management for patients with OSA and moderate-to-severe daytime sleepiness [27]. Significant improvements in objective and subjective sleepiness and several QOL, cognitive, and depression measures as well as blood pressure measurements have been reported in middle aged-adults [28] as well as in the elderly [29]. Bi-level and auto-titrating PAP devices are recommended in patients with pressure intolerance or interface leak. Adaptive servo-ventilation (ASV) is a non-invasive ventilatory therapy that provides positive expiratory airway pressure and inspiratory pressure support, which is servo controlled based on monitoring minute ventilation. In the pivotal trial exploring ASV in patients with heart failure with low left ventricular ejection fraction (LVEF) and CSA, treatment not only had no significant effect on the primary end point (first event of any-cause death, lifesaving cardiovascular intervention, or unplanned hospitalization for worsening heart failure), but all-cause and cardiovascular mortality were both increased [30]. The manufacturer recommendations caution against the use of ASV therapy in patients with symptomatic chronic heart failure and $LVEF \leq 45\%$. Indications for ASV therapy include CSA with or without CSR and complex sleep apnea, characterized by the emergence of central apnea with PAP administration in patients with OSA.

A number of alternative therapies for OSA are available, generally reserved for patients with mild disease or PAP-intolerance. These include mandibular advancement devices [31], nasal expiratory positive pressure therapy [32], and oral pressure therapy [33]. None has been specifically studied in the elderly and data regarding their effectiveness relative to CPAP are limited. Mandibular advancement devices cannot be used in edentulous patients. A large variety of surgical techniques addressing upper airway obstruction are used in the treatment of OSA, but their benefit in elderly populations is unclear [34]. Hypoglossal nerve stimulation, the newest FDA-approved therapy, is effective in selected patients with OSA who fail medical treatment [35]. Clinical trials have limited enrollment to adults ≤ 70 years of age.

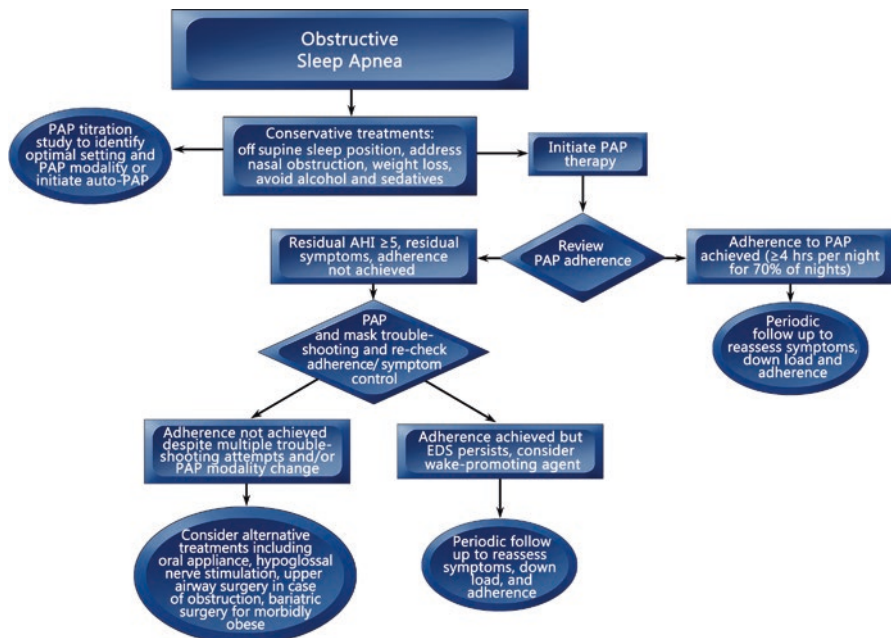


Fig. 19.2 Treatment of OSA

The following conservative treatments should be considered in all patients with OSA and may be adequate in those with mild disease: (1) avoidance of alcohol and sedating medications before bedtime since both worsen upper airway obstruction; (2) weight loss; (3) treatment of nasal congestion or obstruction; and (4) avoidance of the supine sleep position. FDA-approved for the treatment of residual daytime sleepiness in OSA, the wake-promoting agents modafinil and armodafinil improve objective and subjective measures of sleepiness, wakefulness, and perception of disease severity in patients with OSA on PAP therapy and are generally well tolerated [36]. Figure 19.2 illustrates treatment of OSA.

Central Disorders of Hypersomnolence

Central disorders of hypersomnolence feature EDS as the primary complaint that is not caused by other sleep disorders or circadian rhythm misalignment. Although symptoms typically present earlier in life, these disorders are generally persistent and require management in the elderly.

Narcolepsy Type 1

Narcolepsy is the prototypic form of the central hypersomnolence disorders manifesting with chronic, pervasive EDS and signs of REM sleep dissociation [5]. Narcolepsy is classified as narcolepsy with cataplexy (Type 1) or without cataplexy (Type 2). Cataplexy is the most specific among the REM sleep dissociation signs, defined as more than one episode of brief, usually bilateral and symmetric sudden loss of muscle tone with preserved awareness precipitated by strong emotion. Narcolepsy Type 1 is due to a deficiency of hypothalamic hypocretin (orexin) signaling producing central sleep-wake pathway instability. Resulting oscillations produce REM sleep intrusion during wakefulness (cataplexy, sleep paralysis, and sleep related hallucinations) and wake intrusion during sleep (disturbed nocturnal sleep). While some have reported symptomatic improvement with aging, this is not firmly established [37]. Narcolepsy and other central hypersomnias are diagnosed by PSG followed by a multiple sleep latency test (MSLT), a 5-trial study measuring sleep latency in a sleep-conducive environment. Diagnostic criteria for Narcolepsy Type 1 are shown in Table 19.9.

The management of narcolepsy usually requires a combination of pharmacotherapy and behavioral strategies including good sleep hygiene practices, addressing comorbid disorders, and strategic use of caffeine and naps [38]. Narcolepsy pharmacotherapy (Table 19.10) poses challenges in the elderly due to the potential for cardiac and psychiatric adverse effects. Rare complications of traditional stimulants (methlyphendiate, amphetamine, and dextroamphetamine) include hypertension, cardiac arrhythmias, and psychosis. The wake promoting agents modafinil and armodafinil are generally preferred for their more favorable tolerability but are generally less effective. Sodium oxybate is the only approved drug for the treatment of EDS and cataplexy in narcolepsy. Off-label medications for cataplexy include the tricyclic drugs protriptyline and clomipramine, the SSRI fluoxetine, and the SNRI venlafaxine. In patients with comorbid depression, bupropion which has stimulant properties may be considered [37]. Sodium oxybate should be used with caution in the elderly due to potential complications related to its large salt load and risks of confusion and falls during the night. In general, the lowest effective dose targeting the most symptomatic periods of the day is recommended. Comorbid conditions such as OSA should be considered in older patients with narcolepsy presenting with recurrent EDS.

Table 19.9 Diagnostic criteria for narcolepsy type 1

Criteria 1 and 2 must be met:
1. Daily episodes of irrepressible need to sleep or lapses into sleep for at least 3 months
2. Presence of one or both of the following:
a. Cataplexy and a mean sleep latency ≤ 8 min and ≥ 2 sleep onset REM periods on MSLT ^a
b. CSF hypocretin-1 concentration either < 110 pg/mL or $< 1/3$ of mean normative values

Adapted from ICSD-3, 2014

MSLT multiple sleep latency test, PSG polysomnography, CSF cerebrospinal fluid

^aSleep onset REM on the prior night PSG may replace one of those required on MSLT

Table 19.10 FDA-approved agents for narcolepsy

Drug	Usual daily adult dose (mg)	T1/2 (h)	Elderly consideration
<i>Excessive sleepiness</i>			
Modafinil	100–400 q AM or 100–200 bid	15	Palpitations, chest pain, dyspnea, transient T-wave changes. Lower starting dose; half dose in hepatic impairment; BP/cardiac monitoring
Armodafinil	150–250 q Am	15	
Methylphenidate	5–60 mg q d, timing varies by formulation	2–8	Psychiatric effects; abuse potential; avoid in structural cardiac or serious rhythm abnormalities, cardiomyopathy
Dextroamphetamine, Amphetamine/dextro-amphetamine	5–60 mg q d, timing varies by formulation	4–12	Psychiatric effects, abuse potential, avoid in severe arteriosclerosis or arrhythmia, cardiomyopathy, moderate-to-severe HTN, hyperthyroidism; associated with serious cardiovascular events including sudden death in predisposed individuals
<i>Excessive sleepiness and cataplexy</i>			
Sodium oxybate	2.25 g twice at night titrated to 3–4.5 g twice at night	0.5–1	Risk of confusion/falls at night; avoid in patients intolerant of salt load (heart failure, HTN)

Circadian Rhythm Sleep-Wake Disorders

Circadian rhythm sleep-wake disorders (CRSWD) are caused by alterations of the circadian time-keeping system, its entrainment mechanisms, or a misalignment of the endogenous circadian rhythm and the external environment [5]. Advanced sleep-wake phase disorder (ASWPD) and irregular sleep-wake rhythm disorder (ISWRD) are two important CRSWDs to consider in the elderly.

Advanced Sleep-Wake Phase Disorder

Advanced sleep-wake phase disorder is characterized by a consistent advance in the major sleep period which results in earlier sleep onset and offset usually by two or more hours prior to the desired or required sleep time [5]. Patients complain of sleepiness in the evening and/or early morning awakening with difficulty returning to sleep. The prevalence of ASWPD is unknown although it is most frequently encountered in older age groups. Diagnostic criteria are shown in Table 19.11. The diagnosis of ASWPD is based on sleep history and logs or actigraphy for at least 1 week. Typically worn on the wrist and tolerated by older, cognitively impaired individuals, actigraphy monitors rest and activity cycles by measuring gross motor activity. Standardized questionnaires including the Munich

Table 19.11 Diagnostic criteria for advanced sleep-wake phase disorder

Criteria 1–5 must be met:	
1.	Advance in timing of the major sleep period in relation to desired/required sleep and wake times, as evidenced by difficulty staying awake until required/desired conventional bedtime and inability to remain asleep until required/desired wake time
2.	Symptoms are present for at least 3 months
3.	When patients are allowed to sleep in accordance with their internal biological clock, sleep quality and duration are improved with consistent but advanced timing of the major sleep episode
4.	Sleep log and, whenever possible, actigraphy for at least 7 days demonstrate a stable advance in timing of the habitual sleep period
5.	The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

Adapted from ICSD-3, 2014

Chronotype Questionnaire [39] and the Horne-Ostberg Questionnaire [40] can be used to identify ASWPD patients as morning types. Dim light melatonin onset or core body temperature minimum advance by more than 2 h confirm the diagnosis. While PSG is not required, those performed for the evaluation of other sleep disorders should be completed during the patient's habitual sleep period.

Irregular Sleep-Wake Rhythm Disorder

Irregular sleep-wake rhythm disorder is characterized by insomnia and/or EDS in patients who demonstrate an irregular sleep-wake pattern consisting of fragmented and variable amounts of sleep interspersed with wakefulness across the 24 h period [5]. The longest sleep bout is usually less than 4 h and the total sleep duration over 24 h is often normal for age. Diagnostic criteria are shown in Table 19.12. The prevalence of ISWRD is unknown but it is most often observed in patients with neurodegenerative disorders such as Alzheimer's disease. Institutionalized elderly and others who lack exposure to external synchronizing factors, such as bright light and social activities during the day, are particularly at risk. In fact, the challenge of caring for patients with dementia and variable sleep-wake times renders ISWRD a common reason for institutionalization.

The diagnosis of ISWRD is established by the clinical history, review of medications and substance use, and sleep log or actigraphy data. PSG is not indicated unless other sleep comorbidities are suspected. A variety of neurologic and medical comorbidities preferentially affecting the elderly can contribute to EDS and sleep disruption including Parkinson's disease, traumatic brain injury, stroke, inflammatory, infectious and neoplastic lesions involving the hypothalamus or upper mid-brain, hypothyroidism, and metabolic encephalopathy. Similarly, psychiatric disturbances that produce EDS and/or insomnia including atypical depression, bipolar II disorder, seasonal affective disorder, and somatoform, adjustment, and personality disorders should be excluded.

Table 19.12 Diagnostic criteria for irregular sleep-wake rhythm disorder

Criteria 1–4 must be met:

1. Patient/caregiver reports a chronic or recurrent pattern of irregular sleep and wake episodes across the 24-h period characterized by insomnia during the sleep period at night and excessive sleepiness during the day, or both

2. Symptoms are present for at least 3 months

3. Sleep log and, whenever possible, actigraphy for at least 7 days, preferably 14 days, demonstrate no major sleep period and at least three irregular sleep bouts during a 24-h period

4. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

Adapted from ICSD-3, 2014

Treatment

Studies investigating therapies for circadian rhythm disturbances are sparse. Treatment options for ASWPD include timed light exposure and chronotherapy [41]. Timed light therapy consists of bright white light exposure at 2500–4000 lux in the evening from 7–8 PM to midnight [42, 43]. However, treatment responses are variable and limited improvement was achieved in one study involving subjects over 55 years [44]. Chronotherapy, performed by advancing the sleep onset time by 3 h every 2 days until the desired sleep schedule is achieved, has been shown to shift the phase advancement in some cases [45]. Patients with ISWRD typically require mixed modality treatment combining enhanced and scheduled exposure to synchronizing factors of daytime light and physical activity with other behavioral elements, including sleep hygiene, structured bedtime routine, and correction of sleep disruptive environmental conditions such as nighttime light and sound [41].

Parasomnias

Parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep [5]. REM sleep behavior disorder is most relevant for this discussion due to its late-onset, association with neurodegenerative disorders and potential for sleep related injury.

REM Sleep Behavior Disorder

RBD is a REM sleep parasomnia characterized by abnormal behaviors often associated with dream recollection or dream enacting behaviors (DEBs) that may cause injury or sleep disruption [5]. Affected individuals exhibit a broad range of clinical manifestations including vocalizations (talking, singing, screaming, laughing, crying, swearing, mumbling) and motor behaviors ranging from nonspecific repetitive twitching or jerking movements to more complex purposeful behaviors (gesturing,

Table 19.13 Diagnostic criteria for REM sleep behavior disorder

Criteria 1–4 must be met:	
A.	Repeated episodes of sleep related vocalization and/or complex motor behaviors
B.	Behaviors are documented by PSG in REM sleep, or based on clinic history of dream enactment, are presumed to occur during REM sleep
C.	PSG demonstrates REM sleep without atonia
D.	The disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use

Adapted from ICSD-3, 2014

grabbing, dancing, shielding against attack, slapping, punching, kicking, pulling hair, choking, running, crawling, jumping, diving). The eyes are usually closed, resulting in a lack of awareness of the immediate surroundings which limits one's ability to leave the room but places the patient and bed partner at risk of injury. Bruising, lacerations, fractured teeth, skeletal fractures, and subdural hematomas have been reported. Dreams are typically described as action packed, violent, and confrontational, many having a common theme of being attacked by unfamiliar people or animals. Abnormal behaviors generally emerge from the last third of the sleep period when REM sleep predominates. Most patients report RBD symptoms only in response to specific questioning necessitating direct ascertainment during the sleep history [46]. Diagnostic criteria for RBD are shown in Table 19.13.

RBD preferentially affects males with an estimated prevalence of 0.38% in individuals ≥ 70 years [47]. The diagnosis of RBD is frequently followed years later by the development of a neurodegenerative disorder, most commonly one of the α -synucleinopathies including Parkinson's disease, dementia with Lewy Bodies, or multiple system atrophy. In the largest, prospective series, over 80% of RBD patients developed parkinsonism and/or dementia or mild cognitive impairment with a mean latency of 12–14 years from symptom onset [48, 49].

The diagnosis of RBD requires a sleep history that includes bed partner or caregiver observations, review of medications and substance use, and neurological examination assessing for signs of neurodegenerative disorders. Medications and substances that precipitate or aggravate RBD should be carefully elicited. These include tricyclics, monoamine oxidase inhibitors, SSRIs, SNRIs (especially venlafaxine), mirtazapine, cholinesterase inhibitors, bisoprolol, and atenolol [5]. Acute RBD presentation can follow withdrawal from ethanol, benzodiazepines, barbiturates, meprobamate, and pentazocine. RBD must be differentiated from other disorders presenting with DEBs including NREM arousal disorders (somnambulism, sleep terrors, and confusional arousals), OSA, seizures, alcohol or drug use or withdrawal, posttraumatic stress disorder, sleep related dissociative disorder, and malingering. Other diagnostic considerations include sundowning, nocturnal panic, nightmare disorder, and frightening hypnopompic hallucinations.

RBD is the only parasomnia for which PSG is required. PSG recordings with video and bilateral upper and lower extremity and chin EMG demonstrate a loss of normal skeletal muscle atonia during REM sleep [5]. Simultaneous EEG recording is advisable if the clinical history raises concern for sleep related seizures. Brain MRI is

indicated in patients with associated focal neurological complaints specifically assessing for lesions such as brainstem neoplasms, stroke, and limbic encephalitis [50].

Treatment

The treatment of RBD includes implementation of protective measures, discontinuation of precipitating medications/substances, counseling and monitoring for the development of a neurodegenerative disorder, and pharmacotherapy. Critical in the care of patients with RBD is to prevent sleep related injuries [51]. Protective measures include padding furniture, floor mattresses, separate sleep arrangements for bed partners, installation of window/doorway alarms, and stairway protection. Firearms and sharp objects should be removed from the bedroom. Drug-induced RBD will typically resolve with discontinuation of the offending agent. Counseling regarding the potential development of a neurodegenerative disorder is recommended [52]. Monitoring for the development of a neurodegenerative disorder should be performed. In the uncommon event that a lesional etiology is identified, treatment of the underlying disorder should be pursued.

Clonazepam and melatonin are the primary pharmacological treatments for RBD, although randomized controlled trials are lacking [53]. Clonazepam is a long acting benzodiazepine with minimal tolerance or abuse potential that reduces RBD episodes in nearly 90% of cases [54]. The recommended dose is 0.25 mg 30 min before bedtime and titrated to 2 mg as needed. It should be used with caution in patients with OSA, dementia, and gait disorders. Melatonin 3–12 mg at bedtime is also effective and well tolerated based on small case series [55]. Other potentially effective therapies include pramipexole, donepezil, quetiapine, clozapine, sodium oxybate, levodopa, triazolam, temazepam, alprazolam, zopiclone, desipramine, paroxetine, carbamazepine, ramelteon, and Yi-Gan San [56].

Sleep Related Movement Disorders

Sleep related movement disorders are characterized by relatively simple, usually stereotyped movements that disturb sleep or sleep onset and result in nocturnal sleep disturbance or complaints of EDS or fatigue [5]. In this category, RLS is the most important consideration in the elderly.

Restless Legs Syndrome (Willis/Ekbom Disease)

Diagnostic criteria for RLS are shown in Table 19.14. The primary complaint is a strong urge to move the limbs during rest in the evening or at night that is relieved with movement [5]. The urge to move is often accompanied by an uncomfortable sensation in the limbs that is described in a variety of ways including discomfort,

Table 19.14 Diagnostic criteria for restless legs syndrome

Criteria 1–3 must be met:
1. An urge to move the legs usually accompanied by or thought to be caused by uncomfortable and unpleasant sensations in the legs that:
a. Begin or worsen during rest or inactivity such as lying down or sitting;
b. Are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; and
c. Occur exclusively or predominantly in the evening or at night
2. The above features are not solely explained by another condition
3. Symptoms cause concern, distress, sleep disturbance, or impairment in mental, physical, or another area of functioning

Adapted from ICSD-3, 2014

crawling, restlessness, and twitching. Disturbed sleep, difficulty falling back to sleep, leg jerking in sleep, daytime fatigue or sleepiness, depression, and impaired QOL are commonly reported. In early-onset RLS (before age 45), symptom progression is typically slow. Patients with late-onset RLS generally experience more rapid symptom progression that can involve the arms or body.

In a large study exploring the prevalence of RLS using structured interviews in Europe and the U.S., 7.2% of subjects endorsed all diagnostic criteria at any frequency and 2.7% reported moderate-to-severe symptoms at least twice weekly [57]. The prevalence was generally twice as high for women compared to men and increased with age up to 79 years. In a large, European study the prevalence of RLS ascertained by phone interview was 8.2% in subjects ≥ 80 years of age [58]. In addition to female gender, risk factors for RLS include genetics (particularly in the early-onset form), iron deficiency, chronic renal failure, and pregnancy. In addition, RLS has been associated with a number of other conditions including diabetes mellitus, cardiovascular disease, Parkinson's disease and rheumatoid arthritis [59].

Medications and substances known to cause or exacerbate RLS including anti-histamines, antidepressants (except bupropion), thiazide diuretics, dopamine antagonists, caffeine, and alcohol. In addition to genetic predisposition, CNS iron deficiency and dopamine regulation have been implicated as mechanistic underpinnings in RLS.

The diagnosis of RLS is established clinically and sleep testing is not indicated solely for its confirmation. However, periodic limb movements during wakefulness and/or sleep provide objective support for the diagnosis [44]. A physical and neurological examination evaluating for signs of comorbid conditions including peripheral neuropathy, radiculopathy, and myelopathy is required. Laboratory evaluation should rule out commonly associated conditions and include serum iron, total iron-binding capacity, transferrin saturation, and ferritin assessing for iron deficiency.

Restless legs syndrome must be differentiated from a host of medical and neurological conditions including leg cramps, positional discomfort, arthralgias, myalgias, peripheral artery disease, venous insufficiency, sports/orthopedic conditions, leg edema, habitual foot tapping, peripheral neuropathy, radiculopathy, myelopathy, neuroleptic-induced akathisia, and painful legs and moving toes. Complicating matters, the elderly can have both RLS and any one of these mimickers.

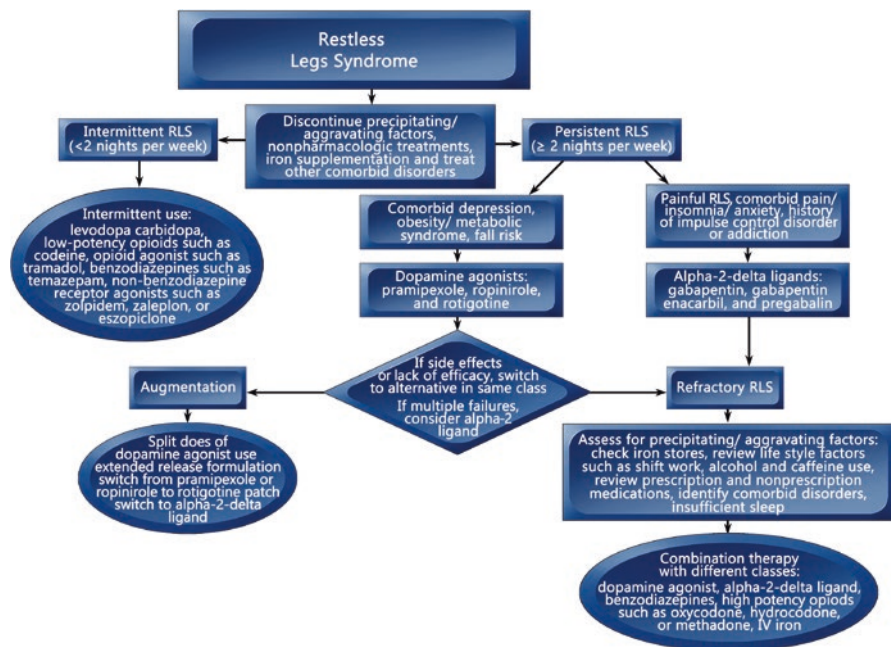


Fig. 19.3 Management of RLS

Treatment

The management of RLS includes nonpharmacologic therapies and pharmacotherapy including iron supplementation (Fig. 19.3). Nonpharmacologic therapies include discontinuation of precipitating and aggravating factors including medications, caffeine, and alcohol, optimization of sleep hygiene, regular exercise, treatment of comorbid medical and sleep disorders, counter-stimulation (massage, baths, ice packs), and cognitive behavioral approaches [60]. Iron supplementation is indicated for serum ferritin ≤ 75 mcg or transferrin saturation $\leq 17\%$ [61]. Treatment consists of ferrous sulfate 325 mg twice daily, preferably on an empty stomach, with vitamin C 100–200 mg to facilitate absorption with repeat laboratory testing after a few months of therapy. Iron supplementation alone will result in a complete remission of RLS in some cases. Intravenous iron therapy may be required in patients unable to tolerate oral formulations.

Pharmacotherapy for RLS includes dopamine agonists, select anticonvulsants, benzodiazepines, and opioids in refractory cases (Table 19.15). Pharmacotherapy is typically considered for those with symptoms at least 2 days per week particularly if sleep quality or duration is compromised and daytime symptoms are present. The dopamine agonists (rotigotine, ropinirole, and pramipexole) and the alpha-2-delta ligands (gabapentin, gabapentin enacarbil, and pregabalin), have demonstrated efficacy in the treatment of RLS [53, 62]. While the dopamine agonists have traditionally been viewed as first-line therapy, the growing awareness of augmentation and impulse dyscontrol render the alpha-2-delta ligands preferred in many cases, including RLS

Table 19.15 Preferred pharmacotherapy for restless legs syndrome in the elderly

Drug	Dose (mg) ^a	T1/2 (h)	Elimination	Considerations
<i>Alpha-2-delta ligands</i>				
Gabapentin enacarbil	600–1200 mg	5–6	Renal	Sedation, dizziness, ataxia, depression, weight gain, headache Dose reduction in patients with reduced creatinine clearance
Gabapentin	100–1200 mg	5–7	Renal	
Pregabalin	0.25–150 mg	6	Renal	
<i>Dopamine agonists</i>				
Ropinirole	0.25–4.0 mg	6–8	Hepatic	Nausea, vomiting, orthostatic hypotension, insomnia, hallucinations, psychosis, impulse dyscontrol, 1st degree AV block, hypertension, palpitations, augmentation
Pramipexole	0.125–0.5 mg	8–10	Renal	
Rotigotine transdermal	1–3 mg	5–7	Renal	

^aStart low and titrate as needed, administered at least 30–60 min before symptom onset, multiple daily doses may be required

associated with pain, anxiety, and insomnia. These agents require monitoring for neurotoxicity and suicidality. Of the alpha-2-delta ligands, only gabapentin enacarbil is FDA-approved with improved absorption over gabapentin. Once the mainstay of RLS therapy, levodopa carbidopa is typically reserved for the treatment of intermittent RLS due to the high prevalence of augmentation. Among the dopamine agonists, the rotigotine patch has the advantage of causing little or no augmentation with long-term use. Benzodiazepines, opioids, combination therapy, and intravenous iron therapy can be considered in patients with dopamine agonist-related augmentation and in refractory cases. Augmentation (worsening or earlier presentation of symptoms due to treatment) can be minimized by avoiding concomitant medications that aggravate RLS, iron supplementation in appropriate cases, and maintaining the lowest effective dose.

ICD-10 codes

F51.01	Chronic Insomnia Disorder
F51.02	Short-Term Insomnia Disorder
G47.33	Obstructive Sleep Apnea
G47.411	Narcolepsy Type 1
G47.22	Advanced Sleep-Wake Phase Disorder
G47.23	Irregular Sleep-Wake Rhythm Disorder
G47.54	REM Sleep Behavior Disorder
G25.81	Restless Legs Syndrome

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Chapter 20

Tremor

Rodger J. Elble

Clinical Pearls

- Rest tremor is most commonly associated with parkinsonism
- Action tremor occurs in postural and kinetic types
- Essential tremor is typically very slowly progressive over many years

Introduction

Tremor is an involuntary oscillatory movement of a body part. Tremor is a very common neurologic sign that is produced by many neurologic and systemic diseases. It is therefore important to perform a careful history and physical examination, looking for other signs and symptoms that lead to a specific diagnosis.

Patients should be characterized in terms of medical history (age of onset, family history, temporal evolution, exposure to drugs and toxins), tremor characteristics (anatomical distribution, activation condition, tremor frequency) and associated systemic and neurologic signs. Tremor is then broadly classified as isolated tremor (tremor is the only physical abnormality) or combined tremor (tremor occurs in combination with other neurologic or systemic signs).

The anatomical distribution of tremor should be carefully documented. Tremor can be focal (only one body region is affected, such as the voice, head, jaw, or limb), segmental (two or more contiguous body parts in the upper or lower body are affected, such as head and arm tremor, or when tremor is bi-brachial or bi-crural), hemi-tremor (when one side of the body is affected), and generalized (when tremor affects the upper and lower body, bilaterally).

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The identification of activation conditions is critical. Rest tremor occurs in a body part that is not voluntarily activated. It is present when a patient makes an effort to relax and is given ample opportunity to relax the affected body part. Rest tremor should be assessed when the body part is completely supported against gravity. In Parkinson disease, rest tremor amplitude almost always diminishes, at least transiently, during purposeful movements, and tremor amplitude typically increases during mental stress (e.g., mental status testing) and while walking or performing voluntary movements with another body part. Rest tremor may occur in advanced essential tremor and dystonic tremor, but these tremors do not subside during voluntary movements.

Action tremor occurs while voluntarily maintaining a posture against gravity (postural tremor) or while performing a voluntary movement (kinetic tremor). Intention tremor occurs when patients perform a precise movement toward a visual target (e.g., finger-nose-finger testing). There is typically little tremor during the initial movement toward the target, but there is a crescendo tremor as the target is approached. This type of tremor is a sign of dysfunction in the cerebellothalamic pathway. It usually occurs in association with other brainstem or cerebellar signs.

Other forms of action tremor are position-specific tremor during the performance of a specific position or posture, task-specific tremor during specific activities (e.g., writing), and isometric tremor during isometric muscle contraction against a rigid stationary object. Re-emergent tremor refers to a rest tremor that subsides for several seconds and then re-emerges when an upper limb is voluntarily moved from a resting pose to an active posture [1]. Re-emergent tremor is common in Parkinson disease.

Most pathologic tremors have a frequency range of 4–8 Hz, so tremor frequency is usually not helpful diagnostically. There are exceptions to this rule. Myorhythmia and palatal tremor are rare forms of tremor at 1–4 Hz, and primary orthostatic tremor typically has a frequency of 13–18 Hz. Tremor frequency may vary among affected body parts, and it is difficult to estimate without accelerometry or electromyography. A smartphone can be used to measure the frequency of head and extremity tremors.¹

Acute and Subacute Tremor Disorders

When tremor develops acutely or subacutely (hours, days or weeks), it is usually due to a drug, toxin or acute medical illness, producing an encephalopathy or focal brain lesion (Fig. 20.1). Consequently, there are nearly always other diagnostic signs. Four tremor syndromes are most common: (1) whole body tremulousness with myoclonus, (2) isolated bi-brachial tremor, (3) rest tremor with parkinsonism, and (4) focal or unilateral tremor with associated focal signs. Psychogenic (a.k.a., functional) tremor is also a consideration when tremor begins acutely and there are no other neurologic signs. Beware that tremor due to neurodegenerative disease

¹play.google.com/store/apps/details?id=com.liftlabsdesign.liftpulse&hl=en

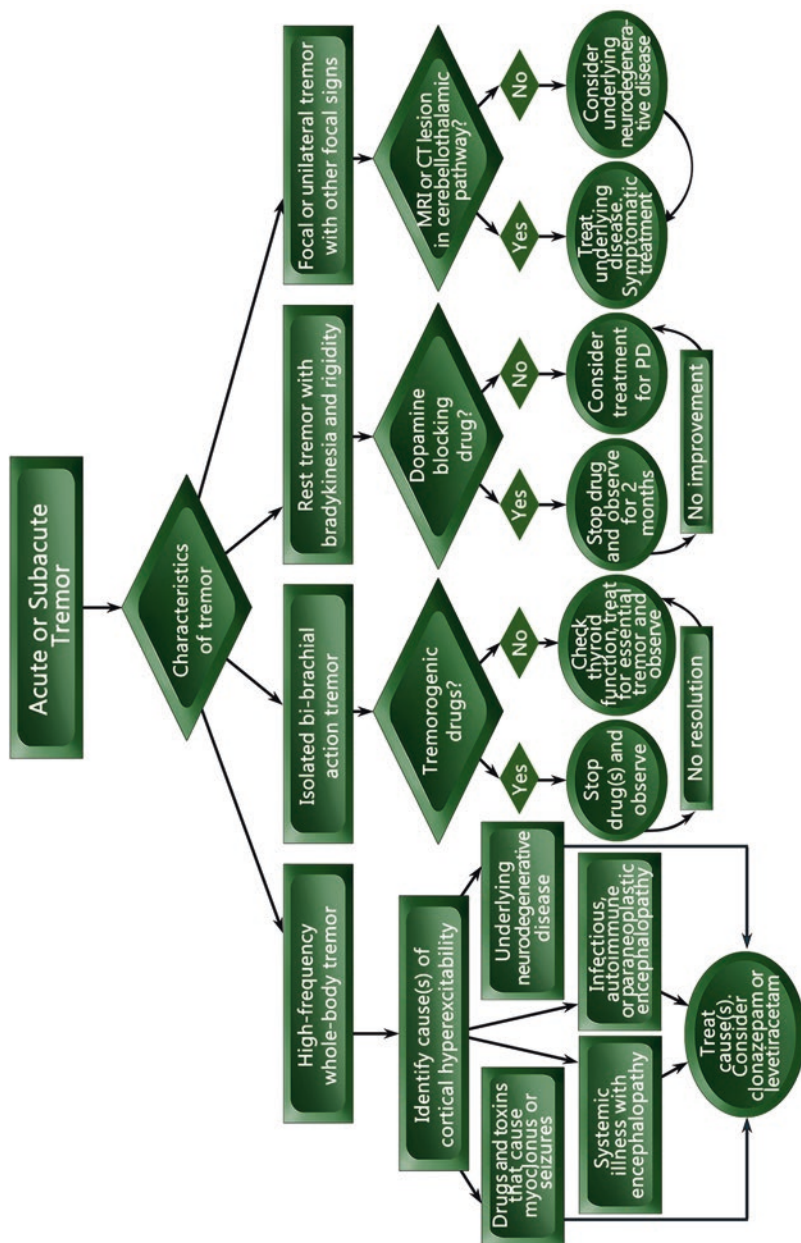


Fig. 20.1 Diagnosis of acute or subacute tremor

(e.g., Parkinson disease) can be recognized suddenly even though it did not begin suddenly. Consequently, a patient's history can be misleading.

Whole Body Tremulousness with Myoclonus

Generalized tremulousness (head-to-toe tremor) is produced by a variety of drugs, toxins, and acute and subacute medical illnesses that increase cerebral cortical excitability [2]. Moreover, chronic neurodegenerative diseases (e.g., Alzheimer disease, Lewy body disease) and hereditary metabolic diseases (e.g., mitochondrial encephalopathies) may cause or predispose one to this type of tremor [3]. The tremor is a rapid 7–20 Hz irregular postural and kinetic tremor that may also occur at rest. This tremulousness is actually rhythmic cortical myoclonus (a.k.a., cortical tremor) and is the most common form of tremulousness in acutely ill inpatients. These patients often exhibit multifocal myoclonic jerks and momentary lapses in limb posture, known as negative myoclonus or asterixis.

When confronted with this syndrome, clinicians should search for systemic illnesses (e.g., liver failure, renal failure, thyrotoxicosis, hypoxia, hypercapnia, sepsis), tremorogenic drugs (lithium, valproate, narcotics, antidepressants, antibiotics), autoimmune and infectious diseases of the central nervous system (e.g., lupus, paraneoplastic disease, ion channel antibodies, HIV encephalopathy) and underlying neurodegenerative disease. Any drug reported to cause tremor, myoclonus or seizures should be regarded as a possible etiology. Treatment is directed at the underlying illness, and benzodiazepines (clonazepam 0.25–1 mg/day) and levetiracetam (250–1000 mg twice daily) are often helpful symptomatically.

Isolated Bi-Brachial Tremor

This tremor syndrome is very common in the elderly, and it is often dismissed as essential tremor, as discussed later in this chapter. However, one should always consider the possibilities of hyperthyroidism and of drug-induced tremor, caused by antidepressants, valproate, lithium, amiodarone, bronchodilators, and many other prescription medications [4].

Rest Tremor with Parkinsonism

Rest tremor with parkinsonism (bradykinesia and rigidity) can be produced by any dopamine receptor blocker (e.g., neuroleptics, antiemetics, metoclopramide) [5]. The parkinsonism produced by these drugs is often indistinguishable from early Parkinson disease, and underlying Parkinson disease should always be considered when a patient develops parkinsonism with a modest dose of atypical neuroleptic or metoclopramide. Drug-induced parkinsonism may take 2–6 months to resolve after withdrawal of the offending drug, and patients should be followed for a re-emergence

of signs due to subclinical Parkinson disease. A dopamine transporter scan may be needed in some patients to determine the presence of underlying nigrostriatal degeneration, most commonly Parkinson disease [5].

Acute Focal or Unilateral Tremor

This tremor syndrome is most commonly caused by lesions in the cerebellothalamic pathway: deep cerebellar nuclei, brachium conjunctivum and contralateral ventrolateral thalamus. Stroke, trauma and demyelinating disease are the most common etiologies. Other focal signs are usually present. The tremor is typically an intention tremor or a combination of rest tremor and intention tremor, called Holmes tremor. Holmes tremor was previously called rubral tremor because it is usually produced by lesions in the vicinity of the red nucleus. These tremors may develop within days of the ictus but more commonly develop weeks, months or occasionally years later, suggesting that deleterious neuroplasticity plays an important role in the pathophysiology of these tremors. These tremors are notoriously refractory to medications (e.g., primidone, propranolol and benzodiazepines). Patients with Holmes tremor should be given a trial of dopaminergic therapy (levodopa or a dopaminergic agonist) [6]. Deep brain stimulation (DBS) and thalamotomy have been used in severe refractory cases [7].

Psychogenic Tremor

Psychogenic tremor often begins acutely and commonly fluctuates in frequency, activation characteristics, or location. It may also relapse and remit [8]. An associated psychiatric illness is frequently not evident.

There are two basic types of psychogenic tremor: coherent type and co-contraction type [9]. The coherent type is a conscious or subconscious rhythmic movement of the affected joint(s). The tremor frequency is usually 6 Hz or less because voluntary rhythmic movement at higher frequencies is very difficult and exhausting. The co-contraction type of psychogenic tremor is usually 6–10 Hz and is produced by a conscious or subconscious coactivation of opposing muscles (extensors and flexors) at the affected joint, producing an enhanced physiologic tremor or so-called physiologic clonus.

Electrophysiology is useful in the diagnosis of both types of psychogenic tremor [10], but diagnosis is often evident by physical exam [11]. Psychogenic tremor decreases when the patient is adequately distracted by cognitive tasks or complex motor tasks. It is nearly impossible to move a joint or multiple body parts simultaneously at two different frequencies that are not integer multiples (harmonics). Therefore, people with the coherent form of psychogenic tremor cannot rhythmically move the same or contralateral extremity at a different frequency, except at subharmonics of the psychogenic tremor frequency. The performance of rhythmic voluntary movement at various frequencies will either suppress the psychogenic tremor or cause its frequency to shift to that of the voluntary movement (entrainment). Similarly, very abrupt voluntary movements (e.g., with the opposite hand) transiently suppress the psychogenic tremor.

The dependence of coactivation tremor on voluntary muscle activation is detected during passive manipulation of the wrist. The amplitude of coactivation tremor is generally mild to moderate and is proportional to the degree of coactivation or stiffness. Coactivation tremor stops during interruptions in coactivation, as when patients are distracted.

To treat psychogenic tremor, one must identify and treat the underlying psychiatric disturbance(s). Unfortunately, the long-term prognosis is frequently poor and depends greatly on the acceptance of diagnosis by the patient and other physicians and therapists. Early diagnosis and therapeutic intervention improve the odds of improvement [12].

Chronic Tremor Disorders

Chronic tremor disorders begin insidiously and are gradually progressive over years. The most common chronic tremor syndromes are essential tremor, rest tremor with parkinsonism (e.g., Parkinson disease), dystonic tremor, and action tremor with ataxia. These four conditions are commonly misdiagnosed due to incorrect characterization of tremor and failure to recognize associated diagnostic signs. It is critically important to distinguish essential tremor and other isolated tremor syndromes (Fig. 20.2) from the combined tremor syndromes (Fig. 20.3).

Essential tremor (ET) is most common. Parkinson disease (PD) occasionally presents with isolated rest or action tremor in the hands or with isolated rest tremor in the lips, tongue, jaw or lower limbs. Electromyography (EMG) is a useful diagnostic test for orthostatic tremor (Fig. 20.3).

Essential Tremor

Essential tremor has not been defined consistently, and this has led to considerable diagnostic confusion in research and clinical practice [13]. Essential tremor is an isolated tremor syndrome of bi-brachial postural or kinetic tremor of at least 3 years duration, with or without head tremor or tremor in other locations, in the absence of other diagnostic neurologic signs, such as dystonia or parkinsonism, and there should be no clinical history of tremorogenic drugs, toxins or hormones. Essential tremor is frequently hereditary, so a family history is common. The required 3 years duration is recommended because this tremor syndrome can be a presenting phenotype of hereditary dystonia and ataxia, and isolated bi-brachial action tremor can be the initial sign or symptom of Parkinson disease. In short, patients may present with bi-brachial tremor that appears to be essential tremor but subsequently develop other signs and symptoms, including parkinsonism, dystonia, ataxia and dementia.

Most patients with essential tremor have mild to moderate tremor that progresses over decades, and a majority of these patients have never seen a physician for their tremor [14]. Nevertheless, some disability from tremor is the rule, and some patients progress to severe disability. Rapid progression over a few years should alert the

clinician to the possibility of a tremorogenic comorbidity such as Parkinson disease or dystonia.

The reported age of onset of essential tremor is usually >40, but this condition develops so insidiously that age of onset is frequently uncertain [15]. Nevertheless, Deuschl and coworkers found that incident hand tremor after age 70 is associated

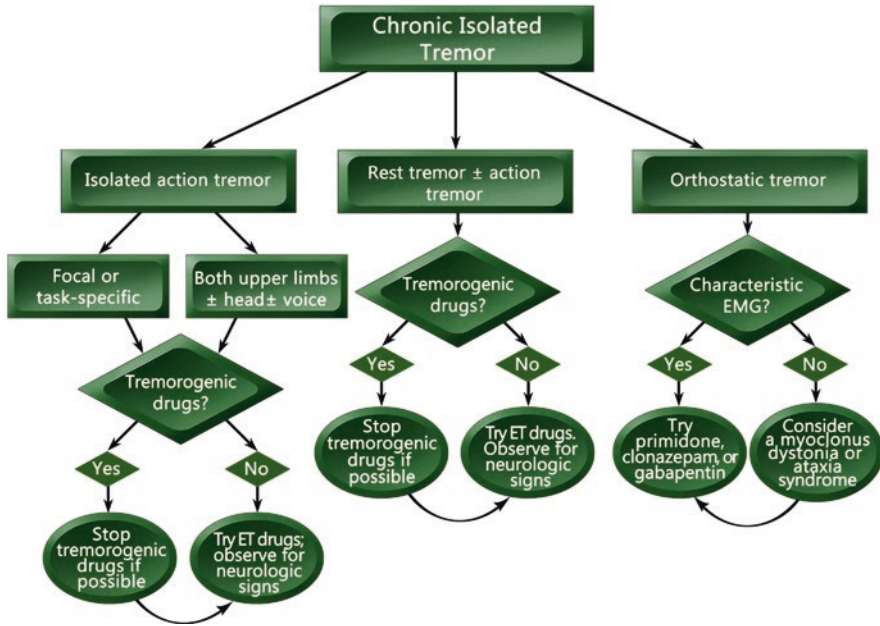


Fig. 20.2 Diagnosis and management of isolated tremor syndromes

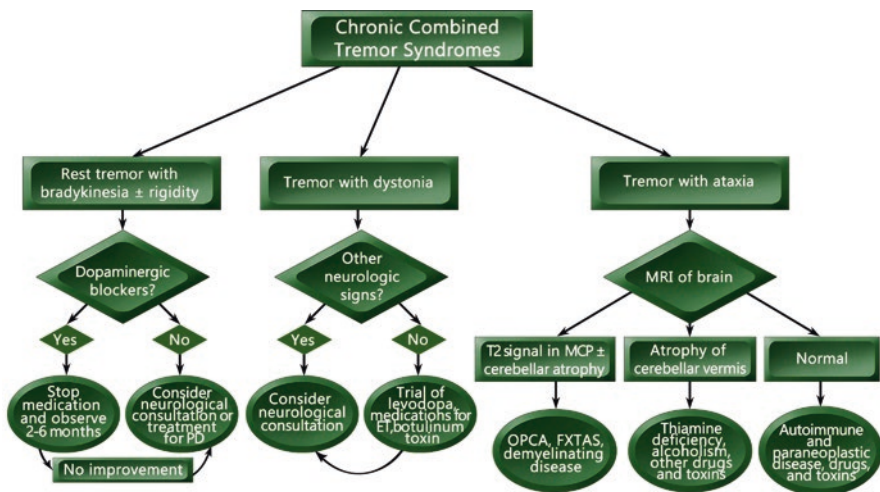


Fig. 20.3 Diagnosis and management of chronic combined tremor

Table 20.1 Drugs for essential tremor and other action tremor syndromes

Drug	Dosage	Common side effects
Propranolol	30–240 mg/day in thrice daily dosing or once daily dosing with extended release	Bradycardia, syncope, erectile dysfunction, fatigue
Primidone	25–300 mg/day in 1–3 divided doses	Nausea, sedation, ataxia, dizziness, and confusion
Topiramate	50–200 mg/day in twice daily dosing or once daily dosing with extended release	Weight loss, anorexia, extremity paresthesias, trouble concentrating, memory loss and nephrolithiasis
Gabapentin	300–2400 mg/day in thrice daily dosing	Dizziness, somnolence, ataxia, nausea

with poor grip strength, cognitive impairment, and increased mortality [16]. There is a small but statistically significant increased risk of dementia in people who develop essential tremor after age 65, and there is also a small increased risk of Parkinson disease (Parkinson disease) in elderly patients with action tremor [17]. Therefore, isolated action tremor in the hands, beginning after age 65, should not be dismissed as essential tremor and instead should be regarded as a possible indication of other age-associated diseases or medication effects.

Treatment should begin with an assessment of the patient's treatment goals and should address comorbidities that affect quality of life, particularly depression. Quality of life scales correlate poorly with essential tremor severity and often reveal a significant psychosocial burden from depression [14]. Counseling may be needed for patients with impaired coping. Self-stabilizing electronic eating utensils are now available (GYENNO, www.gyenno.com and Liftware, www.liftware.com) for patients with mild to moderate tremor.

The pharmacologic treatment of essential tremor is often unsatisfactory. Propranolol, primidone, topiramate and gabapentin have shown efficacy in controlled studies but are often poorly tolerated by older people (Table 20.1) [18]. Each of these medications should be started at a low dosage (Table 20.1) and slowly titrated each week as tolerated and as needed. None of these drugs has a strong dose-response relationship, so dosing is largely trial-and-error [19]. Many patients stop their medication(s) because of cost, side effects or poor efficacy [20]. Patients frequently report a benefit from ethanol, but objective studies of ethanol have revealed modest benefit in most patients [21]. Furthermore, the benefit is short-lasting, and there is rebound exacerbation of tremor as ethanol is metabolized. Most experts do not recommend ethanol for the treatment of essential tremor, but some patients find it helpful at evening mealtime.

Available drugs, including ethanol, reduce tremor by an average of 50%, notwithstanding an occasional dramatic response. A 50% reduction is adequate for mild-moderate tremor but not for severe tremor. For severe tremor, thalamic deep brain stimulation surgery is an FDA-approved option, and this procedure is capable of reducing tremor by >80% [19]. Unilateral noninvasive thalamotomy with gamma knife radiation [22] is still investigational, but unilateral thalamotomy with high-intensity focused ultrasound [23] was recently approved by the FDA.

Parkinson Disease

Rest tremor occurs in the limbs, lips, jaw and tongue of patients with Parkinson disease and rarely in patients with other causes of parkinsonism (i.e., bradykinesia and rigidity), such as progressive supranuclear palsy and multiple system atrophy [24]. Rest tremor in the hand typically consists of a complex “pill rolling” movement of the fingers. Rest tremor is suppressed, at least transiently, when a voluntary movement or posture is initiated, and re-emergent tremor is also common. Bradykinesia and rigidity may be difficult or impossible to detect in patients with tremor-predominant Parkinson disease [25]. The presence of micrographia, hypophonia, decrement in repetitive finger and hand movements, and REM sleep behavior are important clues to the diagnosis. Head tremor and voice tremor are not typical of Parkinson disease and are most consistent with essential tremor or dystonic tremor. However, it is not uncommon for essential tremor and Parkinson disease to coexist in a patient because both are common. Dopamine transporter single-photon emission computed tomography (e.g., ioflupane I-123 SPECT or DaTscan™) may be needed in some patients, but this method will not distinguish Parkinson disease from other causes of nigrostriatal degeneration (e.g., multiple system atrophy).

Bradykinesia and rigidity respond more predictably than tremor to levodopa. The response of tremor to levodopa ranges from complete to nil, and the reasons for this variability are unknown. Large daily dosages of levodopa (800–1200 mg) in combination with carbidopa may be necessary, but one should always start with a low dosage (carbidopa-levodopa 25/100 one half tab thrice daily), and increase the dosage every week or two in half-tab increments as tolerated and as needed. Some patients, particularly women, are very sensitive to levodopa. A dopamine agonist (pramipexole, ropinirole or rotigotine) may be efficacious when levodopa is not adequate [26]. Unfortunately, the agonists are often poorly tolerated by older patients due to hallucinations, drowsiness, impulse control disorders and peripheral edema. Anticholinergics are generally avoided because of cognitive side effects. Propranolol (Table 20.1) is worth trying if there are no contraindications. Amantadine 100 mg twice daily is occasionally beneficial but may cause confusion, hallucinations, livedo reticularis and peripheral edema. Unfortunately, refractory tremor is not uncommon and is one of the indications for deep brain stimulation surgery. The subthalamic nucleus is the preferred target because tremor, bradykinesia and rigidity respond to this therapy, and medication requirements are reduced [27]. Most patients undergoing surgery are younger than 70 and do not have dementia [27].

Dystonic Tremor

Dystonic contractions are frequently tremulous, and patients with focal dystonia of the face, voice or neck frequently exhibit action tremor in the upper limbs. Dystonic tremor can be rest tremor or action tremor, and the dystonic contractions are often missed when the tremor is severe [28]. Consequently, patients with dystonia are commonly misdiagnosed as essential tremor. Patients with subtle dystonia

(abnormal posturing) of the face, neck, voice or upper limbs may exhibit action tremor that is indistinguishable from essential tremor, so a careful search for dystonic posturing and voice irregularities is required. Dystonic tremor may respond to so-called sensory tricks (*geste antagoniste*) in which touching an affected body part reduces tremor and dystonic posturing.

Dystonia is a highly heterogeneous disorder with numerous etiologies, and in most cases, the underlying etiology is unknown [29]. Treatment of dystonic tremor is largely a trial-and-error process. A variety of medications are tried, including those used for essential tremor (Table 20.1), but there is no consistent response to any medication. Intramuscular botulinum toxin injections may be helpful. Deep brain stimulation surgery is reserved for severe refractory cases [27, 30].

Action Tremor with Ataxia

Determining the etiology of late-onset ataxia is a diagnostic challenge. Sporadic and hereditary ataxias must be considered, even when there is no family history [31, 32].

Tremor and ataxia are common features of multiple sclerosis [33], and tremor is occasionally very disabling. These patients usually respond poorly to medications (propranolol, primidone, benzodiazepines, gabapentin) and may ultimately undergo stereotactic surgery with mixed success [34].

Gait ataxia and mild-moderate action tremor in the upper limbs is a classic syndrome of thiamine deficiency in alcoholics, but this syndrome also occurs in chronically ill people that are malnourished (e.g., cancer patients). Atrophy of the cerebellar vermis is seen with magnetic resonance imaging (MRI) or computed tomography (CT scan). When in doubt, give the patient thiamine! In addition, a careful consideration of drugs (phenytoin, lithium, amiodarone, 5-fluorouracil, cytosine arabinoside) and environmental toxins is needed when confronted with this syndrome. This syndrome can evolve subacutely over a few months and may then be associated with no diagnostic clues on MRI. Early diagnosis and treatment are critical.

Paraneoplastic and other autoimmune cerebellar degenerations (e.g., systemic lupus and steroid-responsive encephalopathy associated with autoimmune thyroiditis) also evolve subacutely. The MRI is initially normal, and the syndrome is associated with several autoantibodies [31].

Olivopontocerebellar atrophy is a form of multiple system atrophy (MSA-Cerebellar) that produces action tremor with other signs of ataxia in 25% of patients [35]. Atrophy of the pons and cerebellum may be seen on MRI, often with abnormal T2 signal in the cerebellar peduncles and pons (hot cross bun sign). Intention tremor is also a feature of some autosomal dominant spinocerebellar ataxias (SCA), especially SCA2, SCA8 and SCA12 [32]. The drugs used for essential tremor are often tried but with little or no success. Thalamic deep brain stimulation has been used in a few cases of SCA with mixed success.

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that occurs in older men (age > 50) and rarely women with premutations (55–200 CGG repeats) in the fragile X mental retardation 1 gene [36]. The core features of this syndrome are gait ataxia and action tremor. Associated features may include cognitive impairment, disinhibited behavior, mood disturbance, peripheral neuropathy, parkinsonism, and dysautonomia, producing impotence and urinary and bowel incontinence. Patients may have grandchildren with fragile X mental retardation. MRI usually reveals cerebral and cerebellar atrophy with abnormal T2 signal in the middle cerebellar peduncles (MCP). Genetic testing is diagnostic. The tremor and ataxia are refractory to pharmacotherapy. Thalamic deep brain stimulation has been effective in reducing tremor, but the other aspects of ataxia may be exacerbated by surgery [37].

Uncommon Isolated Tremor Syndromes

Orthostatic Tremor

Primary orthostatic tremor is a generalized 13–18 Hz tremor that occurs when patients stand [38]. The tremor is very rhythmic and uniquely coherent or synchronous throughout the body. Thus, this form of tremor and psychogenic tremor are the only forms of tremor with a diagnostic electrophysiologic test. The tremor may not be visible. However, the tremulous muscle contraction is often palpable, and auscultation of the tremulous muscle contraction reveals a characteristic rhythmic sound similar to a helicopter. This “helicopter sign” is more easily heard on the speakers of an EMG machine during muscle recording with skin electrodes.

The chief complaint is usually unsteadiness while standing, associated with tremulousness in the lower limbs. This unsteadiness is relieved by sitting or walking. Gait and tandem gait are usually normal. Other forms of orthostatic tremor [39] and myoclonus [40] may occur or increase while standing but do not have the characteristic electrophysiologic findings of primary orthostatic tremor. Primidone, clonazepam and gabapentin are often of modest benefit. A handful of severe cases have undergone ventrolateral thalamic DBS with variable success [41].

Focal and Task-Specific Tremors

Tremor occasionally is limited to one body part (e.g., head, chin, voice, limb) or to one specific activity (e.g., writing or playing a musical instrument), and there may be no other neurological signs or symptoms. There is growing evidence that these focal and task-specific tremors are forms of focal dystonia. The treatment approach is the same as for dystonic tremor [30].

Uncommon Combined Tremor Syndromes

Rest Tremor Without Evidence of Dopaminergic Deficit

Fluorodopa PET (positron emission tomography) and dopamine transporter SPECT imaging of the dopaminergic nerve terminals in the striatum are used clinically and experimentally to assess the health of the nigrostriatal pathway in Parkinson disease and other forms of parkinsonism. With the advent of these methods, it was soon discovered that 4–20% of patients enrolled in Parkinson disease research studies did not have abnormal scans [42]. These patients were labeled with the acronym SWEDD (scan without evidence of dopaminergic deficit), and most of them exhibited asymmetric rest and postural tremor. Subsequent studies suggest that a small percentage of these patients do indeed have Parkinson disease (false negative scans), but most have a variety of other conditions including essential tremor, dystonia, fragile X-associated tremor/ataxia syndrome, progressive supranuclear palsy, multiple system atrophy, and psychogenic tremor [43]. The bottom line is that not all rest tremor is Parkinson disease. Re-emergent rest tremor, micrographia, relatively little action tremor, fatiguing or decrement in rapid repetitive hand movements, and a good response to levodopa favor the diagnosis of Parkinson disease, but the diagnosis is difficult, even for experienced specialists [25, 44, 45].

Myorhythmia and Palatal Tremor

Myorhythmia is an unusually slow 1- to 4-Hz tremor that affects various combinations of the face, jaw, throat, tongue, head, eyes, torso and extremities [46, 47]. Virtually all patients have pathology in the brainstem or cerebellum. Stroke is the most common etiology, but demyelinating disease, Whipple disease, celiac disease, Hashimoto encephalopathy, paraneoplastic disease, Wernicke disease, olivopontocerebellar degeneration, viral encephalitis, and collagen vascular disease have all been described. When the etiology is stroke, myorhythmia typically begins weeks to months after the ictus, suggesting that secondary neuroplastic changes release or produce abnormal rhythmic brainstem and bulbospinal activity. Myorhythmia is rare, but it is important to recognize because the underlying etiologies are often treatable. The symptomatic treatment of myorhythmia is generally unsuccessful [46]. Olivary hypertrophy (seen with MRI) and 1–3 Hz palatal tremor (a.k.a., palatal myoclonus) often occur when the cerebello-olivary pathway is affected [48]. This tremor is asymptomatic and is generally one of multiple signs of brainstem or cerebellar pathology.

Oculomasticatory myorhythmia and oculo-facioskeletal myorhythmia are classic signs of Whipple disease affecting the central nervous system [49]. There is a characteristic pendular convergent-divergent movement of the eyes that is synchronous with movements of the face [46]. The classic clinical triad of Whipple disease is the combination of gastrointestinal malabsorption, supranuclear gaze palsy, and oculomasticatory myorhythmia, but isolated central nervous system signs and symptoms

may occur. Whipple disease is treatable with trimethoprim-sulfamethoxazole or with ceftriaxone in patients allergic to sulfa, so the presence of myorhythmia should alert clinicians to the possibility of this rare treatable disease.

Wilson Disease

About 50% of patients with Wilson disease present with neurologic or neuropsychiatric signs and symptoms, and tremor occurs in more than half of these patients [50, 51]. Wilson disease is often considered in the differential diagnosis of tremor, but neurologic Wilson disease rarely if ever starts after age 55. There are no reports of Wilson disease presenting as an isolated tremor syndrome. Signs of dystonia, ataxia or parkinsonism are always present in combination with asymmetric rest, postural or intention tremor in the upper limbs and frequently elsewhere [51].

Tremor Associated with Peripheral Neuropathy

Upper extremity action tremor often occurs in patients with acquired and hereditary (Charcot-Marie-Tooth) demyelinating polyneuropathies [52]. Medications for essential tremor are often tried with little success, and rare cases have undergone stereotactic surgery with mixed success.

Future Therapies

All forms of tremor are relatively refractory to pharmacotherapy. Virtually all forms of tremor emerge from oscillation in the corticobulbocerebellothalamocortical loop, and the ventrolateral thalamic nucleus (ventralis intermedius) appears to be an effective target for any tremor treated with stereotactic surgery [7]. From the standpoint of new drug development, additional understanding of the pathophysiology of tremorogenic oscillation in the corticobulbocerebellothalamocortical loop, particularly the ventrolateral thalamus, is needed to identify targets for drug development. Aside from Parkinson disease, all drugs for tremor were discovered serendipitously or by trial and error.

Many elderly patients do not qualify for DBS surgery due to comorbidities, or they are simply averse to the risks of invasive surgery. Unilateral high-intensity transcranial focused ultrasound is an option for these patients [23].

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Chapter 21

Geriatric Neurological Gait Disorders

Marian L. Dale and John G. Nutt

Clinical Pearls

- Falls that are worse with eyes closed are often due to neuropathy or spinal cord lesions. Check for Romberg sign, proprioception in the toes, and reflexes.
- Bifocals can cause difficulty with balance, particularly on stairs. Consider replacing them with separate glasses for near and far vision.
- A wide based gait is always a sign of a neurological gait disorder.
- Freezing of gait is not always Parkinson's disease.
- Rule out orthostasis as a cause for falls. Consider reduction of anti-hypertensive medications.

Introduction

Disturbances of walking, impairment of balance and falls are common in the geriatric population. They can arise from the musculoskeletal system and multiple sites in the nervous system. There are a great variety of gait and fall patterns. We will offer the care provider ways to diagnose and manage gait and balance disturbances in the geriatric population, emphasizing the more common disorders. Figure 21.1 provides an approach to gait disorders in the elderly.

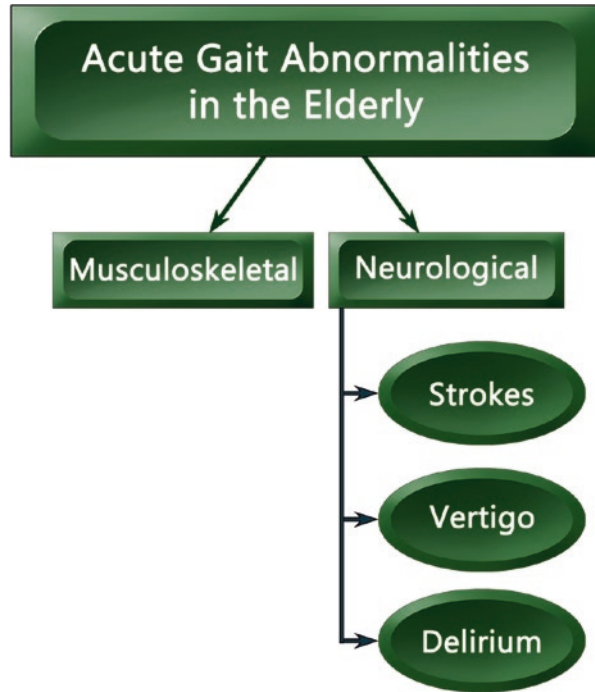
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Fig. 21.1 Approach to gait disorders in the elderly acute gait changes



Gait Exam

The gait exam should carefully evaluate the patient's ability to stand from a seated position, to maneuver around obstacles and through narrow spaces, and to walk in a hallway. Slowed speed of walking is present in most gait disorders. Increased distance between the feet while walking suggests instability and ataxia. The speed, step variability and stability while turning are other clues to stability. Heel-to-toe walking is a further challenge to bring out ataxia. Postural adjustments can be further evaluated with the pull test [1] or the push-and-release test [2]. Reduced arm swing can signify parkinsonism, a cautious gait, or a stroke. Exaggerated arm swing may be seen in dyskinetic or choreic patients. Checking sway when standing with eyes closed evaluates proprioception (Romberg sign, [3]). Walking with eyes closed can detect veering of gait, and walking with rotation of head side-to-side may detect vestibular impairment. Foot drop or waddling indicates distal and proximal weakness, respectively. Limping suggests pain and limitations of range of motion. The neurological exam is used to confirm or refine the impressions from the gait exam.

Acute Changes in Gait and Balance

One distinction that will help the care provider confronting geriatric gait disorders is the speed of onset of the problem. Acute to subacute onset suggests a limited group of disorders.

Acute Gait Dysfunction

Acute causes of gait dysfunction include various musculoskeletal injuries as well as more central neurological insults. Musculoskeletal pain is recognized by an antalgic gait pattern, in which the patient spends less time in the stance phase of gait compared to the swing phase of gait in the affected limb. This pattern indicates pain with weight bearing. Important musculoskeletal causes of acute gait abnormalities include trauma, acute sciatica (M54.30), and occult fracture.

Central, neurological causes of acute gait dysfunction include vascular insults, vertigo and delirium (F05). Vascular insults contributing to acute gait dysfunction include small vessel ischemic lacunar strokes (I69.898), especially when located in the basal ganglia, brainstem or cerebellum (G46.4), and hemorrhagic strokes, including parenchymal bleeds and subdural hemorrhages (I62.00, S06.5X9A). One must have a high index of suspicion for subdural hemorrhages in the elderly, as the symptoms can occur several weeks after relatively minor trauma. The pattern of gait dysfunction in the case of vascular insult is related to the lesion location. For example, a subdural hemorrhage over the motor cortex, cortical or subcortical strokes may all cause a contralateral hemiparetic gait, and midline cerebellar lesions may result in an ataxic gait. Imaging should be pursued for any focal neurological findings on exam. CT scans are best to visualize hemorrhagic or bony structural lesions, and MRI is sensitive for ischemic parenchymal lesions and visualization of the brainstem and cerebellum.) Vertigo can prevent successful ambulation and can arise from peripheral sources (inner ear) or from brainstem and cerebellar strokes. With peripheral vertigo, the nystagmus does not change direction depending on where the patient is looking (is not “gaze-evoked”), but rather, remains unidirectional with a horizontal-rotational appearance. Other reassuring features suggesting that the vertigo is more peripheral in origin include brief episodes with a positional quality (BPPV, benign paroxysmal positional vertigo), and associated tinnitus and hearing loss. When the vertigo is associated with brainstem or cerebellar signs such as diplopia, dysarthria, dysphagia, hoarseness, weakness or numbness of the face, and appendicular ataxia in the arms and legs, the practitioner should be concerned for a more central process and, in the case of acute onset, should obtain emergent imaging.

The pattern of gait dysfunction in delirium is non-specific, and can include ataxia, falls and impulsivity. Concomitant asterixis (elicited by asking the patient to hold out their hands as if they were stopping traffic, and also visible with ankle dorsiflexion) is a sign of a toxic/metabolic disturbance, such in as liver disease. Delirium results from both toxic sources (polypharmacy, alcohol abuse, metabolic derangements) and infections (i.e., urinary tract infection).

Chronic Gait Dysfunction

Gradual onset, chronic gait disorders are more common in the geriatric population. We divide this chronic gait dysfunction into lower-level, mid-level, higher-level and other, non-neurological causes. These categories are based on Hughlings Jackson’s concept of lower, mid-level and higher nervous system function and are intended to provide a schema for understanding the complexity of gait disorders Figure 21.2.

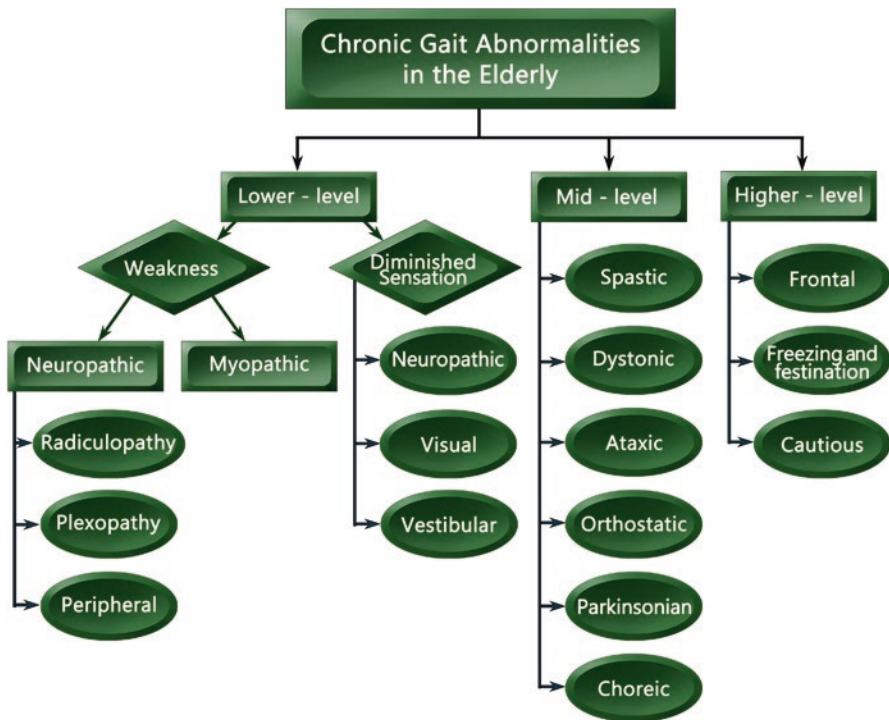


Fig. 21.2 Chronic gait abnormalities in the elderly

Lower-Level Gait Disorders

Lower-level gait disorders consist of disorders of weakness from peripheral roots, nerves and muscle and disorders of diminished sensation from peripheral nerve, vestibular and visual diseases. Lower-level gait dysfunction related to weakness can be further divided into myopathic (G72.9) and neuropathic (G60.3) etiologies. A point of caution: although many patients will describe weakness of the legs as the cause for a gait disturbance, it is often ataxia, parkinsonism, or other movement disorders that are responsible. For weakness to account for a gait disorder, the weakness should be obvious on exam and not mild weakness of hip flexors, which is common in the elderly.

Lower-Level Gait Disorders Due to Weakness

Lower-level gait dysfunction related to weakness is further divided into neuropathic (G60.3) and myopathic (G72.9) etiologies. Lower-level gait disorders due to neuropathic weakness, moving from the nerve roots distally, can be localized to radiculopathies (M54.10), plexopathies, and peripheral neuropathies (G60.3). Chronic radiculopathies are recognized by pain and/or weakness and numbness in a distribution related to a particular spinal nerve root, due to a variety of etiologies. For example, an L5 radiculopathy with foot drop may result in a steppage gait pattern [4], in which the patient flexes the hip excessively to prevent the foot from dragging. In the case of isolated radiculopathy without concomitant brain or spinal cord lesions, patellar and Achilles reflexes are either preserved or diminished, but not exaggerated. When evaluating radiculopathies, it is essential to distinguish true weakness from effort dependent or pain-limited movements of the lower limbs. Conservative management is appropriate for many chronic radiculopathies, but true weakness should prompt neuromuscular consult. For any acute pain and weakness, more prompt neurological and neurosurgical evaluation is necessary. Concomitant bladder or bowel symptoms should also trigger prompt neurosurgical evaluation. Moving distally from the spinal roots, plexopathies are disorders of the lumbosacral nerve plexus related to mechanical compression, vascular disease, infection, prior radiation, or unknown causes. A common example of plexopathy in the elderly patients with concomitant vascular risk factors is diabetic amyotrophy (E13.44), recognized by severe pain and weakness in hip and proximal thigh muscles, generally beginning unilaterally. Finally, more distal peripheral neuropathies (G60.3) can affect gait, resulting in foot drop or the steppage pattern described above. Myopathic gait disorders can be bilateral or unilateral. A bilateral myopathic gait [5] is recognized by the “waddling” appearance, due to weakness of the proximal muscles of the pelvic girdle. Patients with significant bilateral proximal lower extremity weakness of the hip flexors often have difficulty rising from low chairs or vehicle seats. Myopathy (intrinsic muscle disease) is a possible cause of bilateral weakness.

Preliminary laboratory workup for myopathy should include a CBC, complete metabolic panel, CK, myoglobin, ESR, and TSH. A Trendelenburg gait [6], in which the pelvis drops on the side contralateral to gluteal muscle adductor weakness (opposite the standing leg while walking), is a common presentation of a unilateral myopathic gait.

Lower-Level Gait Disorders Due to Diminished Sensation

Lower-level gait disorders due to diminished sensation are divided into neuropathic, visual and vestibular causes. Neuropathic loss of proprioceptive input can result in a sensory gait pattern with excessive foot slap on the ground. A classic example is the gait of tabes dorsalis due to proprioceptive loss and posterior column damage in the setting of untreated syphilis. In severe cases of sensory loss, the gait can appear ataxic or cautious. More commonly, neuropathic sensory loss affecting the large fibers or the posterior spinal columns is recognized by a worsening of balance in the setting of limited visual input. For example, elderly patients may describe falls in the dark or falls in the shower when closing their eyes to wash their hair. This is the basis of the Romberg sign, an inability to stand with the eyes closed. Encouraging nightlight use is an easy, practical step to help reduce falls in this population. Minor sensory disturbances of vibration loss in the toes or decreased touch sensation are not sufficient to produce gait disturbances. Laboratory studies for common treatable causes of neuropathy should include RPR or FTA, A1C or the more sensitive 2-h oral glucose tolerance test, TSH with T4, vitamin B12 with methylmalonic acid, and HIV. Ascertainment of alcohol abuse history is also essential for the workup of neuropathy. Finally, it is important to consider visual (H47.9) and vestibular (H86.90) causes of gait dysfunction. Ophthalmological consult is appreciated for evaluation of diminished visual acuity of uncertain etiology, as well as for management of common conditions such as cataracts and macular degeneration. We find that replacing bifocals with two separate pairs of glasses for near and far vision is helpful for many elderly patients, as bifocals can cause difficulty when descending stairs. In the case of binocular diplopia (in which the double vision resolves when the patient covers an eye), neurological or neuro-ophthalmological consult is ideal. Peripheral vertiginous symptoms contributing to gait dysfunction may benefit from ENT consult and vestibular rehab, including instruction in the Epley maneuver [7]. For all lower level gait disorders, physical therapy and neuromuscular clinic consult are the mainstays of treatment. Imaging and nerve conduction/EMG studies may be recommended in certain cases.

Mid-Level Gait Disorders

Mid-level gait disorders result from diseases that modulate force produced by muscles. Mid-level disorders include spastic, dystonic, ataxic, choreic, and parkinsonian gaits, as well as orthostatic tremor.

Spastic Gait

Spastic gait results from corticospinal tract lesions, including strokes, compressive lesions such as in cervical stenosis, hereditary conditions, and multiple sclerosis or acquired neuro-immunological disorders. In spastic gait disorders tone in the affected limbs is increased and varies with the velocity of movement (the so-called “spastic catch” or “clasped knife” tone, in which the tone is most increased at the beginning and end of the range of motion). Reflexes are often increased. Examples of spastic gait include hemiparetic circumduction [8] (R26.1) in which the affected limb is extended through the knee joint and the foot is planter-flexed, dragging forward in a semicircular motion, and bilateral scissoring gait [9] due to various congenital or acquired upper motor neuron lesions. In the case of acquired deficits, serum and CSF diagnostic workup should be guided by imaging characteristics. For treatment, consider referral to stroke, PM&R (physical medicine and rehabilitation) or movement disorder specialists for targeted chemodenervation with botulinum toxin injections for the most spastic muscles. Referral for botulinum toxin is not appropriate for fixed contractures. It is important to be cautious with muscle relaxant therapy for spasticity, as some amount of spasticity is compensatory for weakened limbs and thus necessary for stability. As for all mid-level gait disorders, consultation of a movement disorder neurologist and referral to physical therapy are beneficial.

Dystonic Gait

Dystonic limbs are recognized by twisted postures of limbs, neck and trunk, and result from a variety of genetic causes, neuroleptic exposures (antipsychotics- even atypical agents, and metoclopramide) illicit drug use (such as methamphetamine) and parkinsonism. For example, a dystonic foot with inversion and plantar-flexion sometimes accompanies Parkinson’s disease. Dystonic gaits (G24.9) can have bizarre phenomenologies, such as the dromedary or “camel like” gait with lordoscoliosis. One of the most striking features of a dystonic gait is its frequent improvement when patients walk backward or use various “sensory tricks” to relieve the dystonia. For example, a patient with excessive forward flexion from captocormia [10] may find initial relief by walking with his hands in his pockets. Lateral flexion of the trunk when sitting or standing but not lying down in Parkinson’s disease is the so-called “Pisa syndrome,” [11] differentiated from scoliosis by the ability to correct the abnormal posture when lying down. For treatment of dystonic limbs, targeted chemodenervation may be useful. Anticholinergics such as trihexiphenidyl can be tried, but may not be tolerated in an elderly population. Similarly, the judicious use of benzodiazepines for painful segmental dystonia can be considered. Consider also a podiatry referral for custom orthotics for dystonic feet with excessive toe flexion. In the case of Parkinson’s disease, proper adjustment of the dopaminergic medication regimen often alleviates foot dystonia, but Pisa syndrome is less responsive to dopaminergic treatment or chemodenervation.

Ataxic Gait

An ataxic gait [12] (R26.0) is recognized by a wide base and associated clumsy, drunken-appearing movements with impaired tandem gait. Ataxic gaits are due to a variety of genetic causes, nutritional deficiencies, toxic insults such as alcohol abuse, metronidazole, phenytoin, and chemotherapeutic agents, as well as immunological and paraneoplastic conditions. In addition to cerebellar damage, ataxic gaits can also result from severe proprioceptive sensory loss in the peripheral nerves or posterior columns of the spinal cord (see section “Lower Level Gait Disorders” above). In addition to neurological consult, it is prudent to obtain an MRI of the brain as well as laboratory workup for treatable causes of ataxia, including vitamin E, vitamin B1, vitamin B12, folate, thyroid and parathyroid studies, anti-gliadin antibodies, and possibly and possibly anti GAD antibodies and paraneoplastic antibodies.

Choreic Gait

Choreic gaits [13] (G25.5), recognized by their irregular dance-like quality, are sometimes confused with ataxia, but the irregular widening of the base and chorea in the limbs distinguishes the two gait patterns. Choreic gaits are due to a variety of causes, including Huntington’s disease, other Huntington’s disease-like genetic syndromes, dyskinesia due to levodopa treatment effect in Parkinson’s disease, tardive dyskinesia from neuroleptic exposure, various immunological and paraneoplastic conditions, metabolic derangements, and certain toxins, such as cocaine. Brain imaging and screening labs are recommended as well as: CBC to rule out polycythemia, plasma calcium, magnesium, glucose, TSH, parathyroid hormone, HIV screen, and ANA, toxicology, with consideration for genetic testing. Tetrabenazine is one option for treating a choreic gait in Huntington’s disease. In the elderly, acute chorea due to elevated blood glucose >350 mg dL generally resolves with a return to euglycemia. If the chorea is induced by levodopa for parkinsonism, one can try amantadine (monitoring for confusion in the elderly) or a gentle levodopa reduction.

Parkinsonian Gait

Classic features of a parkinsonian gait [14] are a stooped posture with short, shuffling steps with decreased stride velocity and diminished arm swing on the more affected side. Generally, this pronounced gait pattern is not the presenting feature of idiopathic Parkinson’s disease and if it is an early sign, other syndromes should be considered. (Diminished arm swing with associated tremor on the affected side can be seen in early Parkinson’s disease, however.) In addition to physical therapy for gait training and extensor muscle stretching and strengthening, one should treat the

underlying bradykinesia with dopaminergic medications if it is affecting activities of daily living or limiting the patient's exercise efforts. In the elderly, carbidopa-levodopa is generally better tolerated than dopamine agonists.

Orthostatic Tremor

Orthostatic tremor [15] (G25.2) is a high frequency tremor of the legs that occurs after standing for seconds to a minute. It is an infrequent but under-recognized cause of gait dysfunction in the elderly, forcing patients to either sit or maintain a quick walking speed to avoid tremor emergence. Patients often report that they feel shaky when standing in lines, and they try to avoid standing still in public. On examination, the high frequency bilateral leg tremor can be seen after standing for seconds to minutes (and sometimes palpated or auscultated). They tremor may also transmit to the arms with forward flexion and transfer of body weight to the upper extremities. This disabling condition is difficult to manage, but may be alleviated with low dose, long-acting benzodiazepines and various anticonvulsants. Patients can be instructed to carry a lightweight portable seat when they are out doing errands. Physical therapy and movement disorder neurology referrals are beneficial.

Higher-Level Gait Disorders

In terms of gait and balance disorders, Hughlings Jackson's highest level disorders refers to gait abnormalities that arise from impaired integration of sensory and contextual information to produce appropriate and purposeful gait and balance synergies. Higher-level gait disorders have been characterized by Elbe as (1) inappropriate (counterproductive) or bizarre limb movement, postural synergies, and interaction with the environment, (2) qualitatively variable performance, influenced greatly by the environment and emotion, (3) hesitation and freezing, and (4) absent or inappropriate (counterproductive) rescue reactions.

Cautious Gait

Patients who perceive imbalance walk with a cautious gait pattern. They often hold their arms in lateral extension and move slowly. They may have a wide stance and appear anxious or overly deliberate. Turns are slow and en bloc. The pattern is that of a normal person walking on a slippery surface such as ice. These patients respond well to reassurance, anxiety management, and physical therapy interventions. The cautious gait pattern may also evolve into a more pathological higher-level gait disorder with time.

Freezing of Gait and Festination

Freezing of gait [16] is a brief, episodic absence or marked reduction of forward progression of the feet despite an intention to walk. Patients may complain of getting “stuck,” and may describe their knees trembling in place. Freezing of gait often accompanies the progression of Parkinson’s disease. In this case, it is important to distinguish between *off* and *on* dopaminergic medication freezing, as the former may respond to medication increases, but the latter generally requires specialized physical therapy. This therapy focuses on teaching the patients to use cues to overcome the freezing (for example, stepping over lines on the carpet or intentionally taking big steps). Certain walkers with stable bases and cuing attachments such as lasers and metronomes are often beneficial. The elimination of footwear with rubberized non-skid soles in the toe box area may also alleviate tripping by the toe catching during the swing phase of gait. Freezing of gait is not pathognomic of Parkinson’s disease but may also occur in the so called parkinsonism plus syndromes such as multiple system atrophy and progressive supranuclear palsy, with frontal lesions including subcortical white matter disease (G21.4), and in normal pressure hydrocephalus. Festination [17], or abnormal quickening and shortening of strides with truncal flexion as though the patient is trying to catch up with their center of mass, may also occur in Parkinson’s disease, and significantly increases fall risk in this population.

Frontal Gait Disorders

Frontal gait disorders [18] present with a slow, shuffling, wide-based gait with frequent initiation failures, inadequate and inappropriate postural responses and freezing. In cases in which the legs demonstrate bradykinesia out of proportion to the arms, the term “lower body parkinsonism” has been applied. Patients with a shuffling, wide based gait and vascular lesions of the basal ganglia or deep white matter on imaging are said to have “vascular or lower-half parkinsonism.” Frontal gait disorders have been so variably termed due to the heterogeneity of the gait phenomenology and associated causes. Accumulating evidence suggests that frontal gait is due to a disruption of either anterior commissural connections between homologous frontal lobe areas or descending projections from the frontal cortex to the thalamus or basal ganglia. Practically speaking, this may result from vascular insults in periventricular, centrum semiovale, anterior corpus callosum, and basal ganglia regions. Additional pathologies to consider are frontal lobe tumors, normal pressure hydrocephalus, and frontal trauma. Normal pressure hydrocephalus (NPH), though itself a contested diagnosis, should still be considered when ventricular enlargement is out of proportion to atrophy on CT or MRI. Neurological referral for consideration for a high volume lumbar puncture (30–50 cc of CSF) or an external lumbar drainage trial should be pursued before more definitive surgical intervention with shunting or endoscopic third ventriculostomy. For NPH workup, it is essential to formally document gait and neuropsychological function pre- and post- interventions (for example, document MOCA and video timed gait). Given the frontal lobe

involvement, frontal gait disorder patients often show executive function deficits, and may display inappropriate impulsivity when walking. To see the full range of gait pathology, patients should be observed during postural adjustments, as well as challenged with obstacles in the walking pathway and concomitant cognitive tasks. A carbidopa-levodopa challenge (up to 1200 mg daily, as tolerated) is reasonable but often unsuccessful in frontal gait patients. Targeted physical therapy with cuing and agility training are the mainstays of treatment.

Other, Non-Neurological Causes of Chronic Gait Dysfunction

There are several other important non-neurological causes of chronic gait dysfunction in the elderly, including disuse, chronic musculoskeletal conditions, orthostatic hypotension, and (much less commonly) psychogenic gait disorders.

Disuse and Chronic Musculoskeletal Conditions

Disuse due to limited walking efforts certainly worsens balance, as well as core and lower extremity muscle tone. Disuse is a common problem in patients who are overly reliant on a motorized scooter or a disabled parking permit. Group exercise classes are generally better for patient motivation and compliance than home exercise. Of course, chronic musculoskeletal conditions such as arthritic knee conditions constrain normal gait, and can be recognized by the antalgic pattern previously described. Patients should be sent for physical medicine and rehabilitation (PM&R) or orthopedic consults, along with ongoing PT.

Orthostatic Hypotension

Orthostatic hypotension (I95.1) due to neurological or cardiovascular causes is a common impediment to normal postural transitions in the elderly population. Patients may complain of feeling woozy or lightheaded on standing, but often simply state they are “off balance.” Reduction of any offending anti-hypertensives and alpha-1 blockers such as tamsulosin is the first step in treatment. Adequate hydration should be encouraged (sometimes difficult in elderly patients with concomitant urinary urgency). Conservative measures such as salt tabs and calf-pumping exercises should be attempted before pharmacological intervention with fludrocortisone, midodrine, or droxidopa. In our experience, compliance with thigh-high compression stockings is poor, though some patients improve with abdominal binders. Patients should be instructed to pause deliberately for a minute after sitting up or standing, and clinicians often must accept some degree of hypertension in order to limit falls due to orthostasis. Physical therapy, movement disorder, and cardiology consults may all be appropriate.

Psychogenic Gait Disorders

Finally, psychogenic gait disorders are a possibility, though relatively rare in the geriatric population. One should be cautious when diagnosing *de novo* psychogenic movements in the elderly; certainly this is a diagnosis of exclusion. For any concern for psychogenic gait in the elderly, movement disorder consultation is essential.

A Brief Checklist to Characterize Falls in the Elderly

Falls can be broadly divided into falls with loss of muscle tone (atonia) and falls with retained muscle tone. Atonic falls are characterized by collapsing to the floor like a rag doll because there is a loss of tone in skeletal muscles. Cardiovascular causes of syncopal falls include orthostatic hypotension (discussed above), vasovagal episodes, carotid sinus syndrome, cardiac arrhythmias and cardiopulmonary arrest. Neurological falls with loss of muscular tone in the elderly are most often due to vertebrobasilar insufficiency (transient posterior circulation compromise) and brainstem strokes.

Neurological falls with retained muscular tone are characterized by toppling like a tree and are due to a variety of neurological etiologies, including strokes, seizures, movement disorders, neuromuscular conditions, sleep disorders (particularly REM behavior disorder causing falls out of bed) and delirium. Treatment for many of these conditions is described above. In the case of movement and neuromuscular disorders, fall frequency can be reduced with appropriate environmental modifications (removing loose rugs, clutter, untrained pets). For REM behavior disorder, bedtime administration of long-acting benzodiazepines such as clonazepam is the standard of care. Benzodiazepines should of course be used cautiously in the geriatric population, with the lowest dose required. Careful evaluation for undiagnosed or untreated sleep apnea before prescription of benzodiazepines is essential. Falls due to delirium resolve with delirium resolution.

With the exception of vasovagal episodes, atonic or collapsing falls are generally more acutely life threatening than falls with retained muscular tone. Because some atonic falls are due to treatable cardiovascular causes, it is essential to consider their origin in the differential diagnosis of geriatric falls.

Treatment

Please refer to Table 21.1 for quick tips regarding preliminary treatment and appropriate consultation for various chronic neurological gait disorders in the elderly. The initial recommended laboratory workup for each gait disorder is listed in the text. Imaging is appropriate for acute, focal neurological deficits, but neurological evaluation prior to imaging is often more cost effective for chronic gait disorders.

Table 21.1 Initial treatment and recommended consults for chronic geriatric gait disorders

	Initial treatment ^a	Recommended consultations
<i>Lower-level</i>		
Diminished sensation	Encourage nightlight, eliminate bifocals	Vestibular rehabilitation, PT, neuro-ophthalmology, ENT, neuromuscular neurologist
Weakness	Optimize nutrition and exercise	PT, neuromuscular neurologist
<i>Mid-level</i>		
Spastic	Cautious use of muscle relaxers, limit vascular risk factors, consider targeted chemodenervation	PT, movement disorder neurologist
Dystonic	Cautious use of anticholinergics, consider targeted chemodenervation	
Ataxic	Consider role of EtOH	
Choreic	If LID: consider amantadine or gentle levodopa reduction	
Parkinsonian	Agility and balance training, treat underlying bradykinesia	
Orthostatic tremor	Cautious trial of long acting benzodiazepine, recommend portable seat	
<i>Higher-level</i>		
Cautious	Anxiety management, group exercise	PT for cuing strategies, psychology, movement disorder neurologist
Freezing of gait and other frontal gait disorders	Consider U-step walker	
<i>Other: non-neurological</i>		
Orthostatic hypotension	Deliberate sit-to-stand, increase hydration, decrease antihypertensives and diuretics, consider salt tabs, fludrocortisone, midodrine, droxidopa	PT, movement disorder neurologist, cardiology
Disuse	Limit unnecessary rollator and handicapped parking use, encourage group exercise	PT
Psychogenic	Encouragement and cognitive behavioral therapy	PT, psychologist

^aSee text for details of initial laboratory workup and appropriate imaging (neurological consult prior to imaging is often more cost effective for chronic gait disorders); chemodenervation = treatment with botulinum toxin; *HD* Huntington's disease, *LID* levodopa induced dyskinesia

ICD-10 Codes

Ataxic gait R26.0
 Carotid sinus syncope G90.01
 Cerebellar stroke syndrome G46.4
 Delirium due to known physiological condition F05
 Dystonia, unspecified G24.9
 Idiopathic progressive neuropathy G60.3
 Myopathy, unspecified G72.9
 Non-traumatic subdural hemorrhage, unspecified I62.00
 Normal pressure hydrocephalus G91.2
 Orthostatic hypotension I95.1
 Other cerebrovascular vasospasm and vasoconstriction I67.848
 Other chorea G25.5
 Other sequelae of other cerebrovascular disease I69.898
 Other tremor, unspecified G25.2
 Other unspecified diabetes mellitus with diabetic amyotrophy E13.44
 Other vascular syndromes of brain in cerebrovascular disease G46.8
 Paralytic gait R26.1
 Radiculopathy, site unspecified M54.10
 Sciatica, unspecified side M54.30
 Syncope and collapse R55
 Traumatic subdural hemorrhage with loss of consciousness of unspecified duration, initial encounter S06.5X9A
 Unspecified disorder of visual pathways H47.9
 Unspecified disorders of vestibular function H81.90
 Vascular parkinsonism G21.4

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3. Romberg test 3.40 minutes. <http://stanfordmedicine25.stanford.edu/videos.html#neurology-exam>
4. Steppage gait 7.28 minutes. <http://stanfordmedicine25.stanford.edu/videos.html#neurology-exam>
5. Myopathic gait 6.07 m. <http://stanfordmedicine25.stanford.edu/videos.html#neurology-exam>
6. Trendelenburg gait 7.16 m. <http://stanfordmedicine25.stanford.edu/videos.html#neurology-exam>

¹We direct the reader to Stanford Medicine's excellent video teaching resource in the gait examination section of the video gallery. Links for other concepts, many from the Springer video atlas and *Parkinsonism and Related Disorders*, are also provided.

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17. Festination. <https://www.youtube.com/watch?v=oSJdgh4N8c>
18. Frontal gait. <https://www.youtube.com/watch?v=o7cIL5XUeu8>

Chapter 22

Delirium

Paula T. Trzepacz

Clinical Pearls

- Acute cognitive impairment is delirium until proven otherwise.
- Search broadly for and rectify all possible etiologies for the delirium.
- Manage quiet and animated delirium the same way because it is an altered state of consciousness irrespective of its overt presentation.

Introduction

The Neuropsychiatric Syndrome of Delirium

Delirium is an acute alteration of consciousness that affects many older persons in the general hospital and nursing homes. The cognitive, behavioral, and perceptual symptoms result from a generalized disturbance of neural network functioning affecting most higher cortical regions, but with intact primary motor and sensory function. Any preexisting brain impairment increases the likelihood of being delirious when precipitating physiological or pharmacological perturbations occur. Therefore, the elderly are at particularly high risk for delirium, related to mild cognitive impairment, cardiovascular and cerebrovascular disease, effects of aging, neurodegenerative disease, or dementia from any cause. The degree of cognitive impairment on admission is linearly related to the risk for incident delirium and delirium severity [1].

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As a rule of thumb based on a variety of studies using different methods, about 20% of patients in the hospital are delirious at any point in time. Ryan et al. [2] evaluated 311 general hospital patients over a 24-h period and found a point prevalence of 19.6% using Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria. Advancing age (34.5% if over 80) and preexisting cognitive impairment were independently associated with even higher rates. Nurses and physicians detected different symptoms: nurses noted inattentiveness, lability of affect and delusions and medical staff noted inattention and short term memory deficits. Delirium rates are higher in ICU, post-operative, palliative care and nursing home patients.

There is not an absence of consciousness in delirium as occurs in coma or stupor, but rather an alteration of aspects of normal consciousness. Normal consciousness consists of a serially time-ordered, organized, restricted, reflective awareness of both self and the environment and is an experience of graded complexity and quantity [3]. Alterations in consciousness affect attention, intention, working memory, awareness, higher level thought, perception and mood/emotion as occurs in delirium. The cerebral cortex is aroused but neural networks that subservise normal consciousness are functioning less than optimally. The person appears to be confused and cannot make sense of the environment or communicate fully with intact focus and comprehension.

There are many etiologies that can precipitate delirium (see Sect. “Etiologies of Delirium”) and the resultant syndrome has essentially the same features. More severe medical illness is a strong factor for producing delirium. However, as Inouye [4] articulated, precipitating factors alone do not account for delirium, rather it is the interplay between those and the threshold for delirium that depends on individual vulnerability. Advanced age is itself a major risk factor for increased vulnerability, likely related to both changes in brain infrastructure and increased incidence of other medical problems and use of pharmaceuticals in the elderly.

Neurophysiology of Delirium

The neuropathogenesis of delirium likely involves a combination of neurotransmitter imbalances, altered neural network connectivity, oxidative stress and neuroinflammation, with delirium resultant from a final common neural pathway that disturbs cortical neural networks [5, 6]. These processes are interrelated and can exacerbate each other.

Acetylcholine is a major neurotransmitter associated with supporting consciousness and neural activity of higher cortical regions. Cholinergic activity from basal forebrain nuclei subserves higher cortical activity including cognition and selective attention, which is integrated with thalamic cholinergic pathways for sensorimotor gating. The thalamus also receives general arousal stimuli from the brainstem [7]. The underlying neurochemistry of delirium probably involves several neurotransmitter imbalances though a deficiency of cholinergic activity with or without an

excess of dopaminergic activity appears to have the most support [8]. This theory is generated from our understanding of neural systems likely involved, preclinical studies, and our knowledge of conditions that induce delirium such as those that can cause metabolic mitochondrial dysfunction. Different cholinergic ascending pathways are important as contributors to cognition, and overall cortical arousal and gating, and for sustaining more complex attentional and cognitive functions with some reciprocal effects with dopaminergic activity [9]. Delirium is associated with generalized EEG slowing, consistent with thalamic dysfunction associated with cholinergic deficiency [10].

Functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG) reports are consistent with altered neural network connectivity in delirium [11, 12], both supporting alterations in thalamic-cortical activity. Disruptions in the default mode network may account for cognitive and other symptoms.

Inflammatory pathways affecting the brain are implicated in delirium and pathology of the basal forebrain cholinergic system predisposes to cognitive effects of neuroinflammation [13] and lower plasma cholinesterase activity and higher inflammatory mediators levels are associated with delirium [14]. There are many reports of cytokine abnormalities associated with delirium or its risk, including various interleukins. A cerebrospinal fluid (CSF) proteomic study reported similar patterns of altered protein expression of several protein families despite differing etiologies for the delirium [15]. Elevations of C-reactive protein, a nonspecific marker of inflammation, have been associated with delirium [16].

Outcomes in the Elderly

Overall, prognosis after a delirium episode is very good and most children and adults return to normal. However, preexisting cognitive impairment especially dementia, frailty or medical comorbidities in older persons increase the risk for delirium as well as a poorer functional recovery and higher mortality post delirium [17, 18]. Falls and fractures are associated with delirium in the elderly [19]. Patients who can recall their delirium experiences may be frightened and concerned they have lost their minds and that it will happen again, requiring education and support [20].

During the index hospitalization delirium is associated with longer lengths of stay and increased mortality in the hospital. Delirious patients may refuse treatments due to fear or inability to comprehend the situation and may be combative. They cannot give informed consent and may be unable to participate in rehabilitative activities like physical therapy.

There is a large literature noting that older persons have poorer functional outcomes after an episode of delirium during the index hospitalization as well as during follow-up after discharge, with increased mortality, reduced independence and increase of dementia diagnosis [21, 22]. However, this association with delirium is usually not addressed as causality of the delirium episode on

outcomes such as being an independent factor using multivariate analyses and correction for confounders [23]. Age, illness severity, preexisting cognitive impairment, impaired arousal in the emergency department, and duration of intensive care unit (ICU) hospitalization may be more relevant to outcomes than incidence of delirium [24–26]. Mortality is often attributable to the underlying medical conditions and their complications, which also precipitated the delirium during an index hospitalization.

Those who have functional deterioration in the months following discharge may have had undetected cognitive impairment prior to the hospitalization, and the medical problems causing a delirium appear to be an independent reason for further brain impairment that results in longer term poor outcomes. Longitudinal studies show that even subtle preexisting attentional or executive function deficits are associated with increased risk of delirium in older persons [27, 28], even without a preexisting diagnosis of MCI or dementia. Comorbid delirium with preexisting dementia strongly predicts worse outcomes [29].

Therefore, delirium should be considered an important marker of poor outcomes in older persons and should signal to clinicians an urgency to determine its causes and aggressively manage and rectify them.

Detection of Delirium

Despite its high prevalence, delirium is underdetected and underdiagnosed. Further, it is misdiagnosed as a variety of other disorders, such as depression, dementia or psychosis, which is problematic because of its high associated morbidity and mortality which requires prompt and accurate diagnosis and management. Being aware of its risk factors and employing simple screening methods can enable better detection in routine care, especially among older persons who are hospitalized.

Screening for dementia at admission using informant based tools such as the AD8 or frailty scales can help identify those at risk for delirium [30].

Clinical Manifestations

Delirium is assessed through history for onset and types of symptoms during clinical interview with the patient and observers, and a thorough mental status examination. Delirium broadly affects cognition plus many other higher cerebral cortical functions affecting thought, language, and affect, as well as motor behavior and sleep-wake cycle. It does not present with primary motor or sensory abnormalities, though if those are affected they might be related to an underlying medical cause for the delirium.

Core Domain Symptoms

A number of studies of delirium phenomenology reveal that certain symptoms are more common and characteristic, and which comprise three core domains: Cognitive, Circadian and Higher level thinking [31]. These persist throughout the episode [32].

Inattention is the cardinal symptom and disproportionately affected as compared to deficits in other cognitive domains: short and long term memory, visuospatial function and orientation. These deficits can be elicited during the interview, observed by staff and more formally assessed using bedside tests. The person may be inattentive, distractible or hyperalert. Disorientation first affects time, then place and then person, with less familiar people not being recognized before family and friends. Not recognizing one's own identity can occur in severe delirium but is rare.

Circadian disturbances affect sleep-wake cycle and motor presentation in ways that are inappropriate for the person at that time of day or night. Motor activity alterations are almost always present and reflect hyperactivity, hypoactivity or a mixed state [33]. These patterns have been documented using 24-h actigraphy which also finds sleep-wake disruptions in delirium [34, 35]. Sleep-wake cycle dysfunction can be mild with restlessness or insomnia or more severe with frequent daytime napping, wakefulness at night or complete reversal and disintegration of the sleep-wake cycle pattern.

Higher level thinking abnormalities can affect thought process, naming ability and semantic language—sometimes referred to as incoherence or confusion because the person is unable to communicate in a meaningful and understandable fashion and cannot correctly comprehend what they are experiencing introspectively or in the environment. Thought process can involve tangentiality and circumstantiality or even loose associations where the train of thought does not connect logically. In delirium's most severe presentations the person may sound aphasic or even mute. Often family and friends who know the person will detect this and worry the person is “demented” or “going crazy.” While listening to a delirious person an interviewer may get a gut feeling of having a disconnected or non-meaningful interpersonal interaction.

Temporal course classically has an acute or abrupt onset, and is a distinct change from baseline for that person. This may be ascertained through history or observed by the clinical team. Symptom severity classically fluctuates over a 24-h period such that the person appears lucid and then inexplicably becomes impaired again. Severe delirium may not have discernable symptom severity fluctuations, especially when it borders on stupor.

Noncore Symptoms

Noncore symptoms occur much less often than core symptoms but can be noticeable and jarring to family and clinical staff. Their presence or absence should not be relied upon to diagnose delirium or dictate therapy, however. It is important to

gather history for the nature of any preexisting noncore symptoms attributable to a dementia, common in more advanced Alzheimer's disease. Psychotic symptoms can be very frightening to the patient and their family, and some remember these following the episode, requiring a reassuring explanation from the clinician.

Psychotic noncore symptoms include abnormal thought content, which can reach delusional proportions but unlike schizophrenia or Alzheimer's disease the delusions are more poorly formed and not well-systematized such that they might change in content over time and can even include bits of context from the clinical situation. These are usually persecutory in nature but may be grandiose.

Perceptual disturbances are usually visual in nature but auditory are also common. Olfactory, tactile or gustatory illusions and hallucinations in a medically ill person usually cue delirium, and occur more often in delirium than in primary psychiatric disorders. Tactile hallucinations suggest anticholinergic toxicity.

Noncore symptoms also include affective lability, which can present as any emotion—sad, anxious, irritable, happy, angry, etc. Characteristically the emotions change rapidly from one to another and are not congruent with the context or conversation. This type of lability is indicative of a medical etiology affecting the brain and uncommon in primary psychiatric disorders except perhaps in severe mania.

Diagnostic Approach

Tools to Detect and Measure Delirium

A variety of tools exist that are used to detect, screen for, diagnose or measure severity of delirium. Not all include descriptive anchors or a breadth of symptoms. Many rate symptoms and features categorically without rating severity. Some are more sophisticated and require advanced understanding of delirium's features and how to interview for accuracy and subtle presence of symptoms, while others are simpler and intended for use among nonspecialists or nurses. Only the more common tools are described here. Figure 22.1 shows a diagnostic approach to delirium.

Brief Tests

The most commonly used brief tool is the 4-item Confusion Assessment Method (CAM) [36] also available as the CAM-ICU version [37]. It is a diagnostic tool with presence or absence rated of its items, but not severity. Though training is not required, its performance metrics improve with rater training, though it both over and under-diagnoses delirium relative to psychiatric interview using diagnostic criteria or more detailed scales in the hands of specialists.

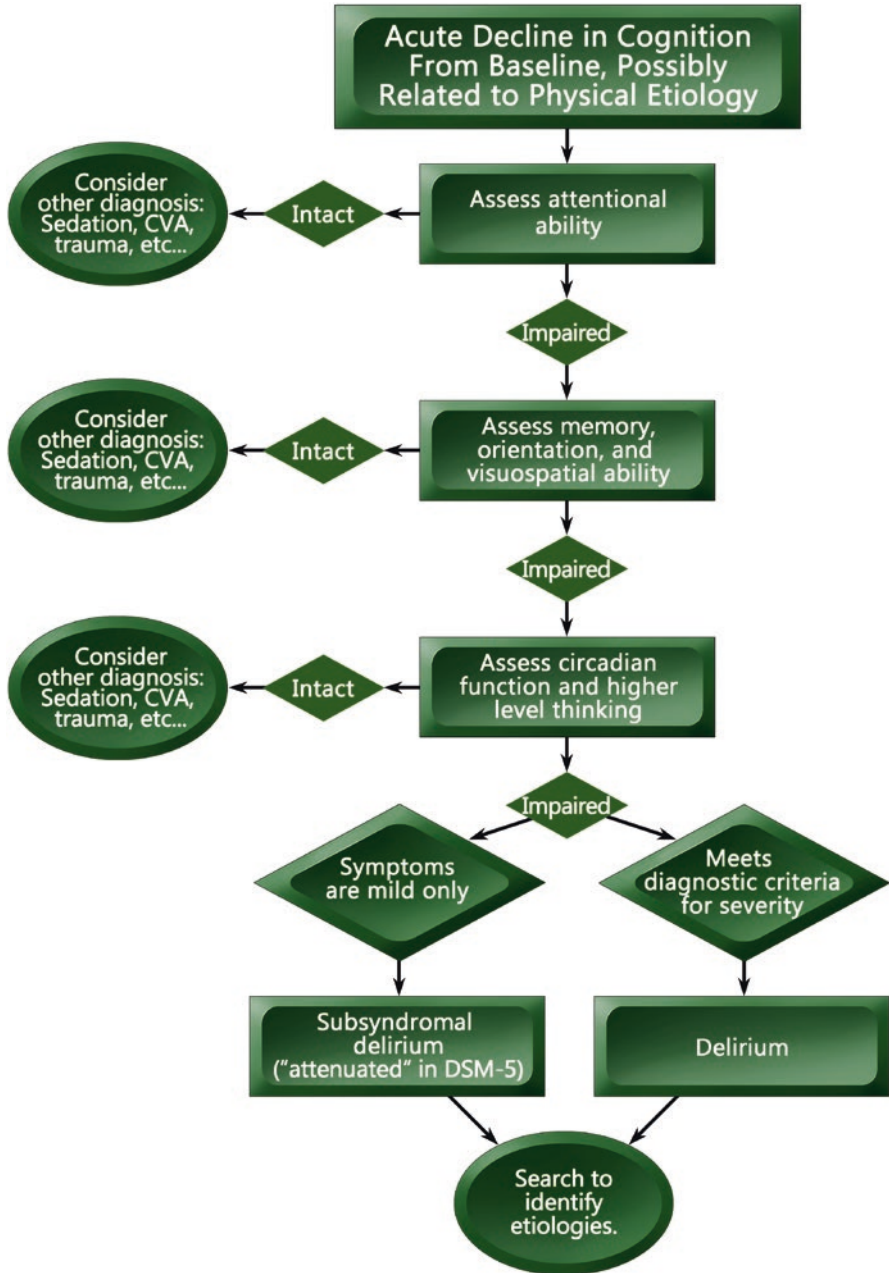


Fig. 22.1 Diagnostic approach to delirium

Some clinicians simply screen for delirium by evaluating attention. Months of the year backwards, an auditory letter vigilance test, digit span, etc. can be used and when performance is abnormal other history and testing for other delirium symptoms can follow. Months of the year backwards had high accuracy for delirium screening detection in older patients [38].

Delirium Symptom Severity Scales

There are two scales that measure a broader range of symptoms that are well-validated and observer rated—the Memorial Delirium Assessment Scale (MDAS) [39] and the Delirium Rating Scale-Revised-98 (DRS-R98) [40]. The MDAS is a 10-item tool using simple Likert scale severity ratings for each item and needs to be used in conjunction with diagnostic criteria for delirium. The DRS-R98 is a 16-item scale with a separately validated 13-item Severity Scale that is used for repeated measures after the diagnosis is already established using the 16-item Total Scale score. The DRS-R98 is unique in that each item has phenomenologically worded descriptors anchoring each item's severity level, and requires the rater to have expertise in interviewing delirious patients.

Bedside Cognitive Tests

Many use multi-domain bedside tests like the Mini-Mental State Examination (MMSE) [41] or the Montreal Cognitive Assessment (MoCA) [42] to evaluate overall cognitive level. These are relatively easy and fast to administer and each has a 0-30 point scale. Both have a ceiling effect though this is worse with the MMSE than the MoCA which is a more challenging test. The MoCA has alternate forms for repeated testing. Neither of these tests will specifically help to diagnose delirium or distinguish it from dementia or other cognitive disorders, rather just establishes a level of cognitive impairment.

The Cognitive Test for Delirium [43] has been designed for and validated in delirious patients and has a high correlation with the DRS-R98 [40].

Etiologies of Delirium

Often delirium has multifactorial etiologies which may be concurrent, serial or complications of another etiology. For example, hypoxemia from pneumonia causes delirium which begins to improve after oxygenation and starting antibiotics, but then benzodiazepines are administered for ethanol withdrawal which worsens the breathing capacity and delirium relapses. Every bodily system needs to be reviewed and considered for etiologies. See Table 22.1 for The Delirium Etiology

Checklist which can be used to ensure a broad consideration of potential etiologies for delirium.

Also every drug taken or recently discontinued that could cause a withdrawal syndrome needs to be assessed as a contributor for delirium. These may have been taken illicitly or prescribed prior to admission or surgery. Ethanol withdrawal may be underestimated in older persons.

Importantly, any drug with sedating (benzodiazepine), anticholinergic, and opioid characteristics are particular culprits and should be reduced or stopped. Anticholinergic medications in frail elderly and palliative care settings increase falls and delirium [44, 45]. Benzodiazepine sedatives are especially problematic in the ICU units where they are over-prescribed and can contribute to difficulty weaning patients from ventilators and causing a vicious cycle with delirium also making weaning difficult [46]. Over the counter medications are often underreported.

Table 22.1

DELIRIUM ETIOLOGY CHECKLIST

This checklist accounts for multifactorial etiologies precipitating or causing delirium in a given patient by using a weighted approach for each of 13 categories. The relative importance all available information (history, examination, and tests) is based on the judgment of the clinician who best knows the patient and then rated in this summary table.

The DEC Worksheet captures more details about the conditions in order to organize the data before rating the categories in the table. Check each box in the category table according to their degree of contribution to the delirium (either definite, likely, possible etc).

For research use the small numbers for column categories and row labels to represent your ratings.

Category	¹ Definite Cause	² Likely Cause	³ Present and Possible Contributory	⁴ Present but Apparently not Contributory	⁵ Ruled Out/Not Present/Not Relevant
¹ Drug Intoxication					
² Drug Withdrawal					
³ Metabolic/Endocrine Disturbance					
⁴ Traumatic Brain Injury					
⁵ Seizures					
⁶ Infection (intracranial)					
⁷ Infection (systemic)					
⁸ Neoplasm (intracranial)					
⁹ Neoplasm (systemic)					
¹⁰ Cerebrovascular					
¹¹ Organ Insufficiency					
¹² Other CNS					
¹³ Other					

DELIRIUM ETIOLOGY CHECKLIST Worksheet			
Drug Intoxication			
1 <input type="checkbox"/> Alcohol	3 <input type="checkbox"/> Opiate	5 <input type="checkbox"/> Hallucinogenic	6 <input type="checkbox"/> Prescribed drug _____
2 <input type="checkbox"/> Sedative-hypnotic	4 <input type="checkbox"/> Psychostimulant	7 <input type="checkbox"/> Other _____	8 <input type="checkbox"/> OTC _____
Drug Withdrawal			
1 <input type="checkbox"/> Alcohol	3 <input type="checkbox"/> Prescribed drug _____		
2 <input type="checkbox"/> Sedative-hypnotic	4 <input type="checkbox"/> Other drug _____		
Metabolic/Endocrine Disturbance			
1 <input type="checkbox"/> Volume depletion	4 <input type="checkbox"/> Uremia	12 <input type="checkbox"/> Hypoalbuminemia	21 <input type="checkbox"/> Hypomagnesiemia
2 <input type="checkbox"/> Volume overload	7 <input type="checkbox"/> Anemia	13 <input type="checkbox"/> Hypoalbuminemia	22 <input type="checkbox"/> Hypermagnesiemia
3 <input type="checkbox"/> Acidosis	8 <input type="checkbox"/> Avitaminosis _____	14 <input type="checkbox"/> Bilirubinemia	23 <input type="checkbox"/> Hypophosphatemia
4 <input type="checkbox"/> Alkalosis	9 <input type="checkbox"/> Hypervitaminosis _____	15 <input type="checkbox"/> Hypocalcemia	24 <input type="checkbox"/> Hypothyroidism
5 <input type="checkbox"/> Hypoxia	10 <input type="checkbox"/> Hypoglycemia	16 <input type="checkbox"/> Hypercalcemia	25 <input type="checkbox"/> Hyperthyroidism
	11 <input type="checkbox"/> Hyperglycemia	17 <input type="checkbox"/> Hypokalemia	26 <input type="checkbox"/> Hypoparathyroidism
		18 <input type="checkbox"/> Hyperkalemia	27 <input type="checkbox"/> Hyperparathyroidism
		19 <input type="checkbox"/> Hyponatremia	28 <input type="checkbox"/> Cushing's Syndrome
30 <input type="checkbox"/> Other _____		29 <input type="checkbox"/> Hypertremia	30 <input type="checkbox"/> Addison's Disease
<input type="checkbox"/> Traumatic Brain Injury			
<input type="checkbox"/> Seizures			
Intracranial Infection			
1 <input type="checkbox"/> Meningitis	3 <input type="checkbox"/> Abscess	4 <input type="checkbox"/> HIV	
2 <input type="checkbox"/> Encephalitis	7 <input type="checkbox"/> Neurosyphilis		8 <input type="checkbox"/> Other _____
Systemic Infection			
1 <input type="checkbox"/> Bacteremia	3 <input type="checkbox"/> Fungal	5 <input type="checkbox"/> Viral	7 <input type="checkbox"/> Urinary
2 <input type="checkbox"/> Sepsis	4 <input type="checkbox"/> Protozoal	6 <input type="checkbox"/> Respiratory	8 <input type="checkbox"/> Other _____
Intracranial Neoplasm			
1 <input type="checkbox"/> Primary	2? <input type="checkbox"/> Metastasis	3 <input type="checkbox"/> Meningeal Carcinomatosis	
Extracranial Neoplasm			
1 <input type="checkbox"/> Site of primary lesion _____		2 <input type="checkbox"/> Paraneoplastic Syndrome	
Cerebrovascular Disorder			
1 <input type="checkbox"/> Transient Ischemic Attack	3 <input type="checkbox"/> Stroke	5 <input type="checkbox"/> Intraparenchymal hemorrhage	
2 <input type="checkbox"/> Subarachnoid Hemorrhage	4 <input type="checkbox"/> Subdural Hemorrhage	6 <input type="checkbox"/> Cerebral Vasculitis	
	5 <input type="checkbox"/> Cerebral Edema	7 <input type="checkbox"/> Other _____	
Organ Insufficiency			
1 <input type="checkbox"/> Cardiac	3 <input type="checkbox"/> Hepatic	5 <input type="checkbox"/> Pancreatic	
2 <input type="checkbox"/> Pulmonary	4 <input type="checkbox"/> Renal	6 <input type="checkbox"/> Other _____	
Other CNS			
1 <input type="checkbox"/> Parkinson's Disease	3 <input type="checkbox"/> Multiple Sclerosis	5 <input type="checkbox"/> Hydrocephalus	
2 <input type="checkbox"/> Huntington's Disease	4 <input type="checkbox"/> Wilson's Disease	6 <input type="checkbox"/> Other _____	
Other Systemic			
1 <input type="checkbox"/> Heat stroke	3 <input type="checkbox"/> Radiation	5 <input type="checkbox"/> Immunosuppressed	7 <input type="checkbox"/> Fractures
2 <input type="checkbox"/> Hypothermia	4 <input type="checkbox"/> Post-operative state	6 <input type="checkbox"/> Other _____	

Imaging

Imaging during delirium evaluation may include a computed tomography (CT) or MRI of the brain to look for mass lesions, strokes, atrophy, trauma, hematoma, or white matter pathology that could be responsible for the delirium. Positron emission tomography (PET) or fMRI brain scans are generally not indicated. There is not a reliable pattern of abnormality using any neuroimaging modality that is specific to delirium per se; rather pathology cues underlying etiologies or risk factors (e.g., atrophy). Ischemic lesions and white matter hyperintensities are associated with increased delirium risk [47] and duration [48].

Imaging of other body parts is used when evaluating for medical conditions that contribute to delirium so that specific therapies can then be instituted to rectify those, thereby indirectly improving delirium.

Electroencephalography

The EEG is characteristically diffusely slowed in delirium [49], with the dominant posterior rhythm falling into the theta or even delta range [50, 51], which can be related to a deficiency of brain acetylcholine. This EEG pattern suggests that dysfunction of the thalamus is involved because it drives the cortical EEG rhythm.

Other less common EEG patterns found in delirium include that for seizures including partial complex status epilepticus and nonconvulsive status epilepticus [52], and confusional migraine when those are the specific etiology. Continuous EEG may be needed to diagnose these patterns.

EEG is usually reserved for difficult differential diagnosis or suspected seizure cases.

Diagnostic Criteria for Delirium

Delirium is considered a major neurocognitive disorder, along with dementia. The International Classification of Diseases (ICD) and DSM versions have delineated specific criteria to support a diagnosis of delirium. Most recently DSM-5 and ICD-10 (see Table 22.2) have been used, though they do not share full concordance for delirium diagnosis and the ICD-10 is less inclusive of cases considered delirious than DSM-5 [53]. Compared to DSM-IV, DSM-5 risks under-diagnosis if awareness in its “A” criterion is too narrowly defined as disorientation to place [54]. However, both DSM-IV and DSM-5 tend to over-diagnose delirium cases because they are less restrictive than DSM-III-R or ICD-10 and may be capturing some sub-syndromal cases.

Table 22.2 Diagnostic criteria for delirium (from DSM-5 and ICD-10)

<i>DSM-5 criteria for delirium</i>	
A.	Disturbance in attention (i.e. reduced ability to direct, focus, sustain and shift attention) and awareness (reduced orientation to the environment)
B.	Disturbance develops over a short period of time (usually hours to days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day
C.	An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception)
D.	The disturbances in A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma
E.	There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or medication), or exposure to a toxin, or is due to multiple etiologies
<i>ICD-10 criteria for delirium</i>	
A.	Clouding of consciousness, i.e. reduced clarity of awareness of the environment, with reduced ability to focus, sustain or shift attention
B.	Disturbance of cognition, manifest by both: <ol style="list-style-type: none"> 1. Impairment of immediate recall and recent memory, with relatively intact remote memory; 2. Disorientation to time, place or person
C.	At least one of the following psychomotor disturbances: <ol style="list-style-type: none"> 1. Rapid, unpredictable shifts from hypoactivity to hyperactivity; 2. Increased reaction time; 3. Increased or decreased flow of speech; 4. Enhanced startle reaction
D.	Disturbance of sleep or the sleep-wake cycle, manifest by at least one of the following: <ol style="list-style-type: none"> 1. Insomnia, which in severe cases may involve total sleep loss, with or without daytime drowsiness, or reversal of the sleep-wake cycle; 2. Nocturnal worsening of symptoms; 3. Disturbing dreams and nightmares which may continue as hallucinations or illusions after awakening
E.	Rapid onset and fluctuations of the symptoms over the course of the day
F.	Objective evidence from history, physical and neurological examination or laboratory tests of an underlying cerebral or systemic disease that can be presumed to be responsible for the clinical manifestations in A-D

The “A” criterion across diagnostic systems is the cardinal one and captures inattention, and also in some diagnostic systems reduced awareness or clouding of consciousness is included. Acute onset of symptoms is required, though this may have occurred prior to the evaluation and an observer is needed to obtain that history.

Unfortunately, the three core domains of delirium are not well represented in current diagnostic systems. However, recently proposed delirium research criteria do require symptoms from each core domain, and when compared to performance

of DSM-5 and ICD-10 in differentiating cluster analysis-defined delirium and non-delirium groups, have high sensitivity and specificity, positive predictive value and outperformed DSM-5 and ICD-10 [53]. While most clinicians will rely on DSM-5 criteria, looking for presence of all three core domain symptoms can enhance diagnosis and clinical detection of delirium.

Subsyndromal Delirium

There is increasing awareness that subsyndromal delirium is worth detecting, though by definition it is less severe than full syndromal delirium, and carries an intermediate level of prognosis between no delirium and delirium. Reports have used different methods to define SSD, including just one or two symptoms which is inadequate to ensure it is syndromally related to delirium. However, studies that used broader assessment of delirium symptoms have discerned that its symptom profile is similar to that of delirium, especially for presence of core domain symptoms, but present at a lower severity [55, 56].

There are no widely accepted diagnostic criteria for subsyndromal delirium (SSD) and DSM-5 simply describes it as “attenuated” without any details. Clinical criteria to diagnose SSD, based on cluster analysis [56], were suggested as mild impairments of attention, orientation, visuospatial ability, sleep-wake cycle, and thought process in the setting of an acute change from baseline.

Differential Diagnosis of Delirium

Because delirium encompasses a wide breadth of neuropsychiatric features and both hyperactive and hypoactive presentations, it can be mistaken for many other conditions, most likely when the examiner does not assess for the full range of symptoms. Misdiagnosis as depression or dementia are common. Referrals to specialists sometimes state “behavior problem” or “incoherence” as the reason.

Distinguishing delirium from dementia alone is an important exclusion criterion for delirium diagnosis though this requires history-taking from someone who knows the patient because these conditions can overlap in their symptom profile and are often comorbid. Most research shows that delirium symptoms overshadow dementia symptoms when they are comorbid [57]. Simple tests of inattention including months of the year backwards can aid in diagnosing delirium even in the setting of comorbid dementia [58].

Therefore, in clinical practice a person is considered “delirious until proven otherwise” and managed as such, with whatever lingering cognitive and behavioral impairments being attributed to dementia or mild cognitive impairment after delirium is resolved. A history of an acute onset of cognitive impairment or worsening of an impaired baseline helps to distinguish delirium from dementia, except

where a large lesion like stroke is the cause. Dementia with Lewy bodies involves visual hallucinations and fluctuating symptom severity and can be misdiagnosed as delirium.

ICD-10

ICD-10 criteria were intended for research and are more detailed than those in DSM-5. They do include more symptoms of the core domains. Being more restrictive than DSM-5, they may tend to diagnose fewer cases which are more specific to delirium, though less sensitive [53] (see Table 22.2).

Therapeutics and Management of Delirium

General Guidance

Delirium is a medical urgency and must be actively managed as soon as possible. All clinical staff should be made aware of the patient's condition and delirium specifically noted in the medical chart. Some institutions have a standardized delirium management protocol that can be ordered. Figure 22.1 shows the key steps in management of delirium.

The first and foremost step in management is to identify risk factors and all possible etiologies (see Table 22.1) and work toward quickly rectifying them. This requires a careful review of the patient's history by reading medical charts, intraoperative records, talking with those who know the patient, pharmacy records, laboratory test results, etc. Testing should be done to address common problems using laboratory testing and more advanced tests such as neuroimaging, CSF examination, EEG and so on tailored to a particular patient.

Treatment includes nonpharmacological and pharmacological methods (see Fig. 22.2).

Overdoses causing delirium include intentional and iatrogenic. These need to be quickly identified and addressed. Intentional overdoses require supportive medical care with monitoring and observation during the period of time that the half-lives and expected elimination times suggest that the drugs taken have cleared the body. Generally the person's delirium clears quickly when the offending agent is metabolized and cleared. This is similar to conservative management of emergence delirium in post-anesthesia recovery following surgery or a procedure.

Iatrogenic drug toxicities can occur due to polypharmacy, doses too high for the person to metabolize, and intentional such as occurs in ICUs. Virtually any drug given at neurotoxic doses can cause delirium.

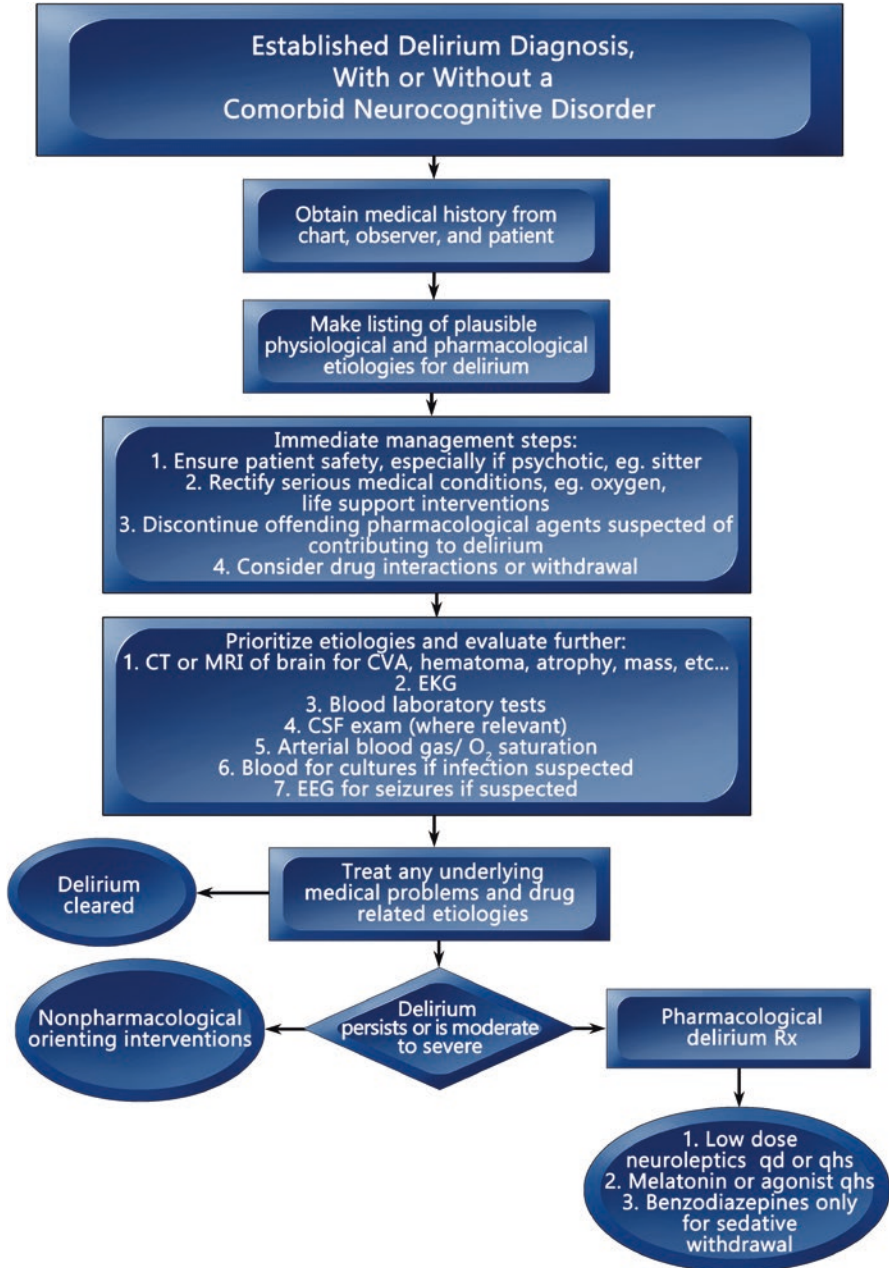


Fig. 22.2 Management of delirium

Special Populations

Intensive care units are problematic situation because patients have a high medical or post-operative morbidity which predisposes them to delirium at a higher rate than in general medical and surgical inpatient units. On the other hand, there is a tendency to overmedicate and sedate these patients, perhaps so they are less troublesome or to help them to not remember the experience [46]. Use of opiates and benzodiazepines are associated with longer delirium duration in ICU patients [59].

A substantial research literature reveals that preferential use of dexmedetomidine during anesthesia and sedation in intensive care reduces delirium incidence [60, 61]. Improving anesthesia care by addressing potentially modifiable factors including blood pressure variability can reduce impact of some operative and postoperative contributors to delirium [62]. Monitoring the depth of anesthesia using the bispectral index to guide anesthesia decreased postoperative delirium such that episodes of deep anesthesia were independently predictive for delirium [63]. Further, lightening the level of sedation (nonbenzodiazepine) in ventilated patients can reduce delirium and enhance respiratory recovery in ICU patients [46]. Additionally, managing pre-operative pain and depression can reduce postoperative delirium [64].

Palliative care, hospice and nursing home populations involve different approaches to delirium treatment than general hospital acute care settings. Often the use of opioids and sedation are carefully titrated in conjunction with use of neuroleptics to balance risk and reduction of delirium in end of life patients [65]. Nursing home patients have a high incidence of dementia so that neuroleptics should be used only short term for delirium due to safety issues because of increased mortality and stroke associated with their use in agitated dementia.

Nonpharmacological Approaches

Simple bedside techniques may help delirious patients to reorient but by themselves cannot alter the depth or resolution of delirium. Family photos, clocks and calendars in view are easy to implement. Ensuring that hearing aids, eyeglasses, dentures, and so on are being used is important. Reminders by staff that the person is in the hospital and is sick can also help and be reassuring. Physical restraints should be avoided and sitters, including family, employed instead. Adapting the environment to better represent normal daylight and nighttime quiet and darkness to enhance sleep is important including in ICUs [66], where single bed rooms are less associated with delirium [67].

More beneficial is prophylaxis of delirium in elderly by identifying modifiable risk factors early during the admission [68]. Studies differ on which are best to focus on and remediate, but these include dehydration, urinary tract infection, pain, depression, hypertension, sensory impairment, immobilization, sleep deprivation, medications, sleep apnea, etc. A daily multicomponent nurse intervention random-

ized study found significantly lower delirium incidence, prevalence, and severity vs. controls by addressing orientation, sensory deficits, sleep, immobilization, hydration, nutrition, drug review, oxygenation, and pain [69].

Pharmacological Approaches to Delirium Treatment

There are no medications with an approved indication to treat delirium and there is a paucity of adequately powered double blind, randomized placebo-controlled clinical trials. There are over 30 prospective trials, either open label, comparative and single or double blind randomized for acute efficacy or prophylaxis [70, 71]. Neuroleptics are the most studied drugs for acute efficacy and prophylaxis, and about 75% of patients receiving them acutely for delirium have a positive response [71]. A variety of other medications have been tried for delirium, most without sufficient supporting evidence [72].

Because of its high morbidity and associated mortality medications are used to manage the delirium symptoms. Psychiatrists and palliative care physicians are generally less conservative regarding use of psychotropic medications in delirium than geriatricians. Haloperidol remains the practice standard in palliative care [73] and general hospitals. Some reserve neuroleptics for agitated patients but it is not recommended to withhold treatment from any delirium patient based on their motor presentation.

Prophylactic and acute treatment have been studied, where agents may have differential efficacy for one of these uses.

Neuroleptic

Neuroleptic (also called antipsychotic) agents include conventional and atypical agents. Haloperidol is most often used though many atypical agents are preferred as they carry lower risk of extrapyramidal side effects. Those include quetiapine, olanzapine, risperidone and aripiprazole. Doses in delirium are usually much lower (e.g., 0.25–0.5 mg haloperidol) than those used for primary psychiatric disorders. Bedtime or twice daily dosing is common for starting treatment with titration up or downward according to symptom severity. Clinicians usually report fast response after treatment initiation. Most are used orally though parenteral administration is possible with haloperidol and some atypicals.

Reports indicate good tolerance and suggest similar efficacy for haloperidol, olanzapine, risperidone, and quetiapine though trial designs have often been a limitation [74]. A number of comparative trials report similar efficacy among neuroleptics [69, 75, 76].

A double blind placebo controlled prophylaxis trial using low dose haloperidol found significantly decreased delirium severity and duration and decreased length of stay (LOS), though the trial was not adequately powered or dosed to detect delirium incidence differences [77]. A randomized blinded placebo-controlled trial of prophylactic risperidone in subsyndromal delirium found significant reduction in

delirium occurrence [78]. A double-blind randomized placebo controlled prophylaxis trial of intravenous haloperidol in 457 elderly surgical ICU patients found significantly lower delirium incidence, longer time to delirium and more delirium-free days and shorter LOS [79]. A double-blind randomized placebo-controlled prophylaxis trial of low dose olanzapine in 495 elderly joint replacement surgery patients found significantly lower incidence of postoperative delirium in the treatment group [80].

One potential issue using neuroleptics in elderly is the risk of death and stroke reported with their chronic use in agitated demented patients, resulting in a boxed warning by FDA. Therefore, neuroleptic use for delirium should be acute and temporary, and patients not discharged on neuroleptics without planned reassessment. Serious adverse events associated with neuroleptic use for delirious hospitalized elderly were low (0.9% in 2834 cases) where aspiration pneumonia was most common and no deaths were reported [81].

Benzodiazepines

Benzodiazepine use in elderly is a risk factor for delirium and their use avoided. Benzodiazepines should not be used to treat delirium with the exception of managing alcohol and sedative-hypnotic withdrawal states, seizures and end of life situations.

Sleep Agents

Melatonin and ramelteon (melatonin agonist) administered at bedtime are reported to prevent delirium in controlled studies [82–84], possibly through addressing the circadian component of delirium [85]. Though not all studies found positive results on reducing delirium incidence for melatonin [86], it is an endogenous neurochemical and its low adverse event profile makes it useful to try clinically.

Cholinesterase Inhibitors

Given the evidence that cholinergic activity deficits may underpin delirium, cholinesterase inhibitors have been evaluated for value in delirium treatment. No efficacy has been found for acute treatment, possibly related to slow onset of action due to long half-lives of agents administered orally.

A multicenter double blind placebo-controlled randomized prophylaxis trial was stopped prematurely due to increased mortality in the rivastigmine group [87].

ICD-10 Codes

- F05 Delirium, not induced by alcohol and other psychoactive substances
- F05.0 Delirium, not superimposed on dementia, so described
- F05.1 Delirium, superimposed on dementia
- F05.8 Other delirium
- F05.9 Delirium, unspecified

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Chapter 23

Assessment and Management of Psychiatric Symptoms in Neurodegenerative Disorders

Kasia Gustaw Rothenberg

Clinical Pearls

- Neuropsychiatric symptoms (NPS) (apathy, irritability, agitation, depression, delusions, hallucinations, anxiety, disinhibition, aberrant motor behavior, sleep disturbances, appetite and eating abnormalities) can manifest themselves at all stages of neurodegenerative disorders (NDD). NPS often cluster, tend to be persistent, are associated with excess morbidity and mortality, and contribute to patients' distress and caregiver burden.
- Currently, there are no FDA-approved medications for the treatment of NPS with the exception of pimavanserin approved for the treatment of delusions and hallucinations in Parkinson's disease.
- Cholinesterase inhibitors (ChEIs) may reduce the emergence of NPS and have a role in their treatment.
- Although used "off label", a large number of antidepressants, mood stabilizers, typical and atypical antipsychotics are prescribed for NPS. An ongoing assessment of benefit versus harm should continue throughout the course of treatment with periodic consideration of withdrawing the medication.

Introduction

Behavioral and psychological symptoms of dementia (BPSD) also termed neuropsychiatric symptoms (NPS) commonly accompany neurodegenerative diseases (NDD) [1]. Cardinal psychiatric symptoms such as depression, apathy, psychosis or agitation complicate the clinical presentation of Alzheimer's disease (AD) and

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Parkinson's diseases (PD) and some are considered core symptoms of frontotemporal dementia and dementia with Lewy bodies (DLB). NPS are near universal among patients with NDD, thus almost all patients with AD experience at least one of them during the course of their illness [2]. NPS are usually assessed by comprehensive psychiatric evaluation but more structured tools like the Neuropsychiatric Inventory (NPI) commonly used in the setting of trials can be of help in clinical practice [1]. The group of common and debilitating NPS include: apathy, irritability, agitation, depression, delusions, hallucinations, anxiety, disinhibition, aberrant motor behavior, sleep disturbances, appetite and eating abnormalities [1, 2]. NPS can manifest themselves at all stages of NDD (especially when a dementia syndrome is present), often cluster, tend to be persistent, are associated with excess morbidity and mortality contribute to patients' distress and caregiver burden. NPS are linked to increased healthcare use, costs, and institutionalization [3, 4].

The neurobiology of NPS is extremely complex. Dysfunction in frontal-subcortical and cortico-cortical networks was proposed as a model of NPS [5]. Dysfunction in ascending monoaminergic systems involving serotonin, norepinephrine and dopamine, glutamate-mediated excitatory neurotoxicity, tau-mediated pathology, and inflammation may play a role in the occurrence of NPS in NDD [6–8].

Despite the significant burden of these symptoms, there are few recommended, evidence-based treatments including pharmaceuticals [4, 9]. Pharmacotherapy in the geriatric population in general is challenging due to age-associated changes in pharmacodynamics and pharmacokinetics as well as high rates of medical comorbidities and use of concomitant medications, which increases risk for polypharmacy, drug-drug interactions, and adverse drug effects [9]. Additionally, there are risks attributed to use of antipsychotics, antidepressants, anxiolytics and/or mood stabilizers in elderly, and specific risks to patients with dementia [4]. Psychotropics, especially antipsychotic medications, may alleviate certain NPS, but may have severe adverse effects including increased risk of involuntary movements, cerebrovascular events, falls, and death [9].

AD treatments like cholinesterase inhibitors (ChEIs) may reduce the emergence of NPS and have a role in their treatment. These agents may delay initiation of, or reduce the need for other drugs such as antipsychotics thus ChEIs should be initiated, optimized and maintained for the management of both cognitive symptoms as well as NPS [7].

Currently, there are no FDA-approved medications for the treatment of NPS in NDD with the exception of pimavanserin which was recently approved for the treatment of psychosis in the course of PD [10]. Although used "off label", a large number of antidepressants, mood stabilizers, typical and atypical antipsychotics are prescribed for behavioral disturbances in persons with NDD [4, 11].

Parallel to robust efforts in pharmacological trials there is an ongoing need to assess and verify existing, as well as create new nonpharmacologic behavioral strategies. Cohen-Mansfield [12] conceptualizes behavioral disorders in the course of NDD as representing unmet personal needs such as pain and other somatic discomfort, and need for social contact. Those needs should be recognized and addressed

by nonpharmacologic interventions. Therapeutic approaches should be individually tailored to each patient with NPS using behavioral management techniques, caregiver education and support, problem solving and communication skills training, music therapy, aromatherapy, and modified cognitive-behavioral and interpersonal therapies.

With few exceptions initiating pharmacotherapy should occur only after eliminating underlying medical or environmental factors and should be limited to cases where nonpharmacologic measures have failed [11, 12]. All patients should be carefully monitored for development of adverse events and side effects during a time-limited treatment course; symptoms often resolve over time regardless of medication use [11]. An ongoing assessment of benefit versus harm should continue throughout the course of treatment with periodic consideration of withdrawing the medication [4, 13].

This chapter addresses NPS in AD and PD. The principles are applicable to other NDD where supporting data are less well-developed.

Depression of Alzheimer's Disease

Depression of AD concept was defined as a depressive syndrome with prominent decreased affect, irritability, agitation, and anxiety, diminished attention and fatigue but less evidence of guilt and suicidality than major depressive episode [14]. Depression of AD is relatively common (affecting up to 50% of persons with AD) and persistent. More than 50% of untreated depressed patients with AD remaining depressed at 1-year follow-up [14]. A National Institute of Mental Health Work Group developed diagnostic criteria for depression of AD (NIMH-dAD) (Table 23.1) which were derived from DSM-IV criteria for major depression, with some adjustment. The number of symptoms required for a diagnosis of depression was decreased as well as duration and frequency of depressive symptoms. The decreased ability to think and concentrate was eliminated. The criteria for anhedonia were modified to focus on decreased affect and pleasure associated with social and other activities. Social isolation/withdrawal and irritability were added as new symptoms [15].

Despite the widespread antidepressant use (almost 50% of patients with dementia are on antidepressants) there is mixed evidence regarding the benefits for depressed AD patients. Use of antidepressants in AD and other NDD is based on rules developed for major depressive disorder pending better evidence for depression of Alzheimer's disease.

Cholinesterase inhibitors studies provide some evidence of benefit in improving mood. Among the NPS in AD apathy and depression (followed by aberrant motor behavior) are the ones to improve [16, 17]. Donepezil reduces behavioral symptoms, particularly mood disturbances and delusions, in patients with AD [7]. A withdrawal study by Holmes et al. [17] provided additional evidence to support the use of donepezil in the treatment of NPS (including depression) in patients with mild to moderate AD with marked NPS. Discontinuation of donepezil corresponded

Table 23.1 Criteria for depression of Alzheimer's disease

Three (or more) of the following symptoms must be present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms must either be (1) depressed mood or (2) decreased positive affect or pleasure
1. Clinically significant depressed mood
2. Decreased positive affect or pleasure in response to social contacts and usual activities
3. Social isolation or withdrawal
4. Disruption in appetite
5. Disruption in sleep
6. Psychomotor changes
7. Irritability
8. Fatigue or loss of energy
9. Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt
10. Recurrent thoughts of death, suicidal ideation, plan or attempt
B. All criteria are met for Dementia of the Alzheimer Type (DSM-IV)
C. The symptoms cause clinically significant distress or disruption in functioning
D. The symptoms do not occur exclusively in the course of delirium
E. The symptoms are not due to the direct physiological effects of a substance
F. The symptoms are not better accounted for by other conditions such as major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of Alzheimer disease, anxiety disorders, or substance-related disorders

Adapted from: Teng E, Ringman JM, Ross LK, Mulnard RA, Dick MB, Bartzokis G, Davies HD, Galasko D, Hewett L, Mungas D, Reed BR, Schneider LS, Segal-Gidan F, Yaffe K, Cummings JL; Alzheimer's Disease Research Centers of California-Depression in Alzheimer's Disease Investigators. Diagnosing depression in Alzheimer disease with the national institute of mental health provisional criteria. *Am J Geriatr Psychiatry* 2008 Jun;16(6):469-77

with worsening of NPS and increased in caregiver distress as compared with those who remained on the treatment. Optimization as well as maintenance treatment with ChEIs should be considered as an important step in the management of depression of AD.

As for antidepressants the American Psychiatric Association (APA) recommends their use in persistent depression in patients with dementia. Selective serotonin reuptake inhibitors (SSRIs) are preferred because of their favorable safety profile [18]. Sertraline, citalopram or escitalopram in low doses are the most appropriate first-line agents (Fig. 23.1). The dose can be increased weekly, if tolerated, to a maximum of 150 mg of sertraline or 40 mg of citalopram per day with close monitoring of side effects. Although improvement should occur within 4-6 weeks at the target dose, a longer period may be required for full effect. Other SSRIs like fluoxetine and paroxetine are not recommended as a first-line due to debatable efficacy and unfavorable (mostly anticholinergic) effects [19]. If patients do not respond to SSRI, switching to a different agent or augmenting a treatment with second agent may be considered. Especially for patients who have psychotic symptoms or

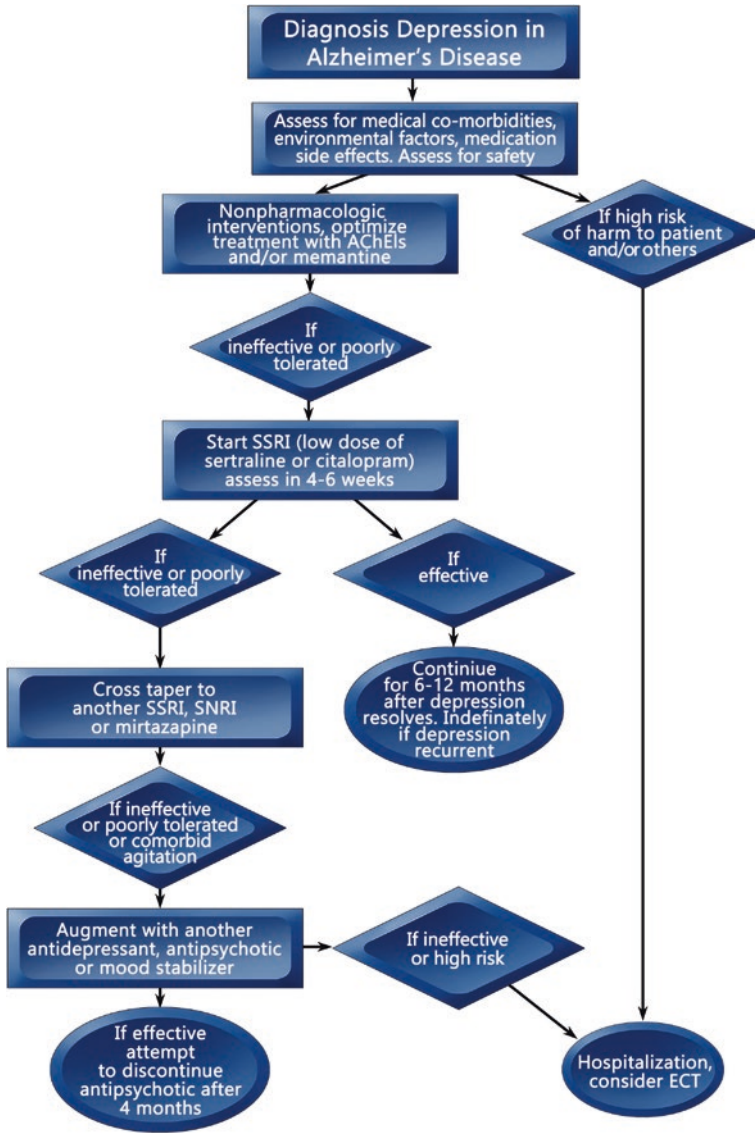


Fig. 23.1 Treatment of depression in Alzheimer's disease

agitation along with depression, an atypical antipsychotic in a small dose might be considered [4, 20, 21]. An anticonvulsant in smaller doses (the best evidence is for carbamazepine) might be considered as additional therapy to an antidepressant if there is moderate or severe agitation [22]. Switching to an antidepressant of a

different class (as opposed to augmentation) is recommended in cases of severe side effects induced by initial medication. Preferred second-line agents are selective norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine or duloxetine, or antidepressants with a mixed pharmacology (mirtazapine, bupropion). Tricyclic antidepressants are not recommended due to lack of convincing evidence and the occurrence of side effects including anticholinergic complications. Psychiatric hospitalization should be considered an option in severe cases.

For patients with severe, refractory depression, electroconvulsive therapy (ECT) might be considered, especially if there is risk of self-harm or harm to others [19]. There is evidence for ECT as an effective and well-tolerated option for treating depression in people with dementia [23].

Therapeutic interventions are being recognized as a valuable treatment modality as well. Interpersonal psychotherapy (IPT) modified to address the needs of older adults with mild cognitive deficits (IPT-CI) [24], cognitive-behavioral therapy (CBT) adapted for depressed older adults with mild stages of dementia [25], home delivered problem adaptation therapy (PATH), or problem solving skills and caregiver training [26] were proved to be beneficial.

Apathy of Alzheimer's Disease

Apathy, often assessed concomitantly with mood symptoms, should be rather considered a disorder of motivation. Conceptualized as diminished goal-directed activity in the domains of behavior, cognition and emotion, apathy is considered one of the most common NPS in AD with a 5-year prevalence of 71%. It can cluster with other NPS and is associated with higher costs and burden of care [2, 27]. Apathy criteria are available (Table 23.2). Diminished motivation in comparison to the patient's previous level of functioning should be noted. Diminished motivation should be observable most of the time for a period of at least 4 weeks and accompanied by additional symptoms like loss or diminished goal-directed behavior or/and cognitive activity or/and emotion. Symptoms should cause clinically significant impairment in personal, social, occupational, or other important areas of functioning and cannot be exclusively explained by physical and/or motor disabilities, diminished level of consciousness or the direct physiological effects of a substance [28]. The approach to management of apathy is illustrated in Fig. 23.2.

Growing evidence suggests that apathy in AD is a manifestation of dysfunction of dopaminergic circuits between the basal ganglia, anterior cingulate, and other frontal cortex structures involved in motivation and reward.

ChEIs may improve symptoms of apathy in AD [16], and symptoms may worsen after discontinuation of ChEIs [17]. Optimization and maintenance treatment with ChEIs is a crucial step in the management of apathy of AD.

Table 23.2 Criteria for apathy in neurodegenerative disorders

A: Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others
B: Presence of at least one symptom in at least two of the three following domains for a period of at least 4 weeks and present most of the time
Domain B1—Behaviour: Loss of, or diminished, goal-directed behavior as evidenced by at least one of the following:
Initiation symptom: loss of self-initiated behavior (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)
Responsiveness symptom: loss of environment-stimulated behavior (for example: responding to conversation, participating in social activities)
Domain B2—Cognition: Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:
Initiation symptom: loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs)
Responsiveness symptom: loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the person's residence, neighbourhood or community)
Domain B3—Emotion: Loss of, or diminished, emotion as evidenced by at least one of the following:
Initiation symptom: loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect)
Responsiveness symptom: loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news)
C: These symptoms (A–B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning
D: The symptoms (A–B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication)

Adapted from: Mulin E, Leone E, Dujardin K, Delliaux M, Leentjens A, Nobili F, Dessi B, Tible O, Agüera-Ortiz L, Osorio RS, Yessavage J, Dachevsky D, Verhey FR, Cruz Jentoft AJ, Blanc O, Llorca PM, Robert PH. Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry* 2011 Feb; 26(2):158–65

Psychostimulants including methylphenidate and modafinil have been used to treat apathy in AD. Methylphenidate acts by blocking the dopamine transporter and norepinephrine transporter, leading to increased concentrations of dopamine and norepinephrine within the synaptic cleft. Methylphenidate (but not modafinil) proved to be effective in reducing apathy in AD in a small cross over trial and larger, multicenter, double-blind controlled trial for Alzheimer's Disease Methylphenidate Trial (ADMET) [29].

In ADMET, methylphenidate (20 mg daily for 6 weeks) was associated with a significant reduction in apathy symptoms. Adverse events and side effects were modest. Methylphenidate treatment may have clinical utility in treating apathy of AD.

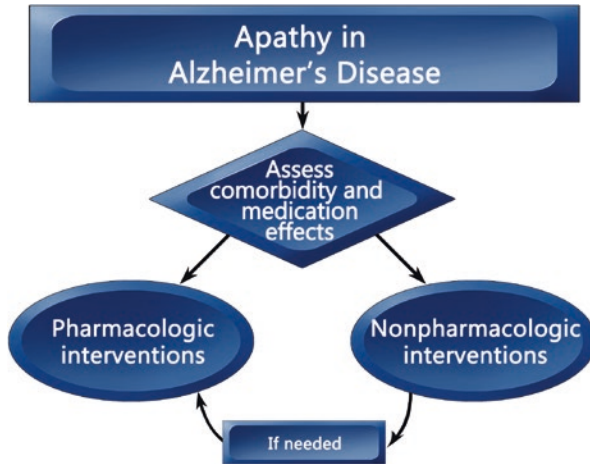


Fig. 23.2 Approach to management of apathy

Psychosis of Alzheimer's Disease

Estimates of the incidence of psychosis in AD range widely from 10 to 75%. (Table 23.3) provides the diagnostic criteria for psychosis of AD. The common psychotic symptoms are delusions and hallucinations followed by misidentification phenomena. Hallucinations are predominantly visual. Auditory phenomena especially of a schizophrenic quality are rare in AD [30]. Delusions in the course of AD are typically paranoid, non-bizarre, and simple. Delusions tend to recur or persist for several years in AD patients. Vivid hallucinations and delusions tend to diminish in intensity in the course of cognitive decline with reduced insight and decreasing ability for verbal expression [30].

Patients with delusions are significantly older, with more advanced age at onset and cognitive impairment, a more severe stage of dementia, and tend to be more depressed than AD patients with no delusional symptoms. Delusional patients showed a higher grade of disability in basic and instrumental activities of daily living [31].

Psychosis of AD is believed to be the result of dysfunction of frontal lobe circuitry with contributions from neurofibrillary tangles in limbic structures as well as neurochemical abnormalities including the cholinergic deficit and dopaminergic dysfunctions. Delusions cluster with hallucinations, agitation/aggression, depression mood, apathy, irritability, aberrant motor activity, sleep disturbances, and eating disorders. More severe cognitive impairment and faster rate of cognitive decline are associated with and predictive of hallucinations and delusions in patients with AD. Parkinsonism is concerned as predictive symptom of imminent psychotic symptoms in AD.

ChEIs may reduce or/and postpone the need for the psychotropics. In a few studies, donepezil reduced delusions, hallucinations and agitation in the majority of subjects.

Memantine appears to provide modest benefit for the management of AD psychosis and has a favorable safety profile. In a pooled, retrospective analysis of data from three placebo-controlled trials in moderate to severe AD, memantine was linked to significant reduction in psychosis, agitation, and aggression [32].

Table 23.3 Diagnostic criteria for psychosis of AD [30]

(a) Characteristic Symptoms
Presence of one (or more) of the following symptoms:
1. Visual or auditory hallucinations
2. Delusions
(b) <i>Primary Diagnosis</i>
All the criteria for dementia of the Alzheimer type are met ^a
(c) <i>Chronology of the onset of symptoms of psychosis vs. onset of symptoms of dementia</i>
There is evidence from the history that the symptoms in Criterion A have not been present continuously since prior to the onset of the symptoms of dementia
(d) <i>Duration and Severity</i>
The symptom(s) in Criterion A have been present, at least intermittently, for 1 month or longer. Symptoms are severe enough to cause some disruption in patients' and/or others' functioning
(e) <i>Exclusion of schizophrenia and related psychotic disorders</i>
Criteria for Schizophrenia, Schizoaffective Disorder, Delusional Disorder, or Mood Disorder With Psychotic Features have never been met
(f) <i>Relationship to delirium</i>
The disturbance does not occur exclusively during the course of a delirium
(g) <i>Exclusion of other causes of psychotic symptoms</i>
The disturbance is not better accounted for by another general-medical condition or direct physiological effects of a substance (e.g., a drug of abuse, a medication)
Associated features: (<i>Specify</i> if associated)
With Agitation: when there is evidence, from history or examination, of prominent agitation with or without physical or verbal aggression
With Negative Symptoms: when prominent negative symptoms, such as apathy, affective flattening, avolition, or motor retardation, are present
With Depression: when prominent depressive symptoms, such as depressed mood, insomnia or hypersomnia, feelings of worthlessness or excessive or inappropriate guilt, or recurrent thoughts of death, are present

^aNote: For other dementias, such as vascular dementia, Criterion B will need to be modified appropriately

In patients with more severe psychotic symptoms which do not respond to ChEIs or/and memantine, antipsychotic medications are used. Olanzapine (up to 10 mg daily) has shown benefit in managing delusions and hallucinations, anxiety and agitation in AD patients [33]. Aripiprazole (5–10 mg/day) was efficacious and relatively safe for psychosis associated with AD, significantly improving psychotic symptoms and agitation [34]. Risperidone (mean doses of 1.5 mg daily) treatment proved efficacious for psychosis of AD in several studies [20, 35].

Quetiapine is commonly used for off-label indications such as NPS of AD. It is believed to have a lower incidence of serious side effects such as extrapyramidal symptoms and tardive dyskinesia when compared with other antipsychotics. Quetiapine can be used in a wide range of doses. Sedating properties are of some use in certain clinical situations in NDD [36]. Results may vary across studies but most show modest benefit for psychosis and agitation with an acceptable side effect profile (Fig. 23.3).

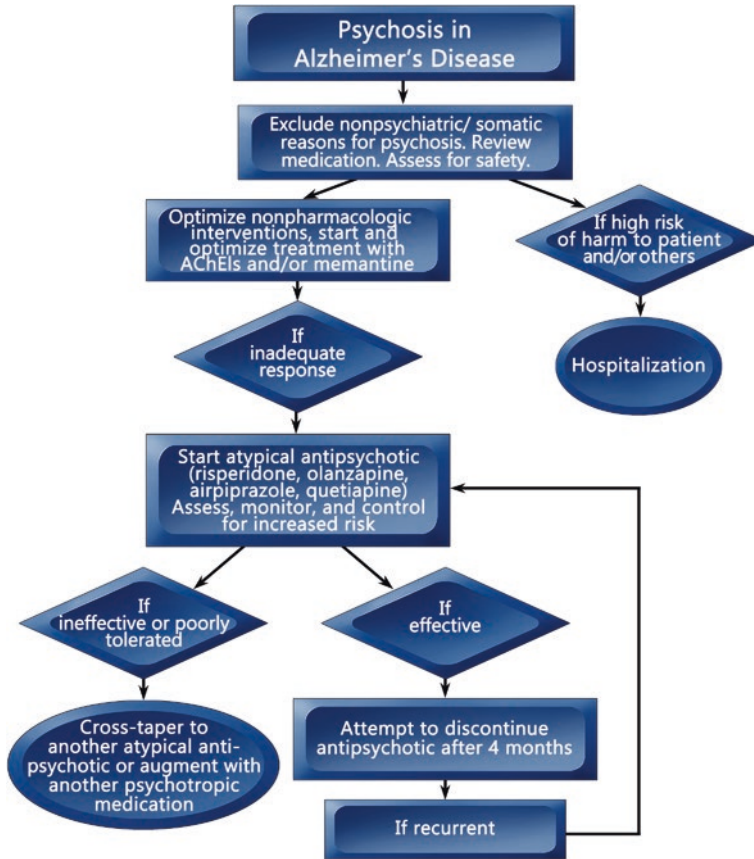


Fig. 23.3 Treatment of psychosis in Alzheimer's disease

Next generation atypical antipsychotics such as pimavanserin—approved for treatment of delusions and hallucinations in PD [10]—may be useful for treatment of psychosis of AD.

Atypical antipsychotics appear to have some impact in reducing psychosis as well as agitation in AD with the best evidence to support risperidone use. Carefully monitored and relative brief courses of antipsychotics are recommended.

Agitation in the Course of AD

Agitation as a symptom of AD is common (prevalence ranges from 20 to 60%) and highly disruptive. Agitation commonly clusters with aggressive behavior and tends to co-occur with sleep disorders, delusions, hallucinations, anxiety and dysphoria [12, 37].

Table 23.4 provides the International Psychogeriatric Association (IPA) criteria for the definition of agitation in cognitive impairment [38].

Table 23.4 International Psychogeriatric Association definition of agitation in cognitive impairment

A. The patient meets criteria for a cognitive impairment or dementia syndrome (e.g. AD, FTD, DLB, vascular dementia, other dementias, a pre-dementia cognitive impairment syndrome such as mild cognitive impairment or other cognitive disorder)
B. The patient exhibits at least one of the following behaviors that are associated with observed or inferred evidence of emotional distress (e.g. rapid changes in mood, irritability, outbursts). The behavior has been persistent or frequently recurrent for a minimum of 2 weeks' and represents a change from the patient's usual behavior
(a) Excessive motor activity (examples include: pacing, rocking, gesturing, pointing fingers, restlessness, performing repetitious mannerisms)
(b) Verbal aggression (e.g. yelling, speaking in an excessively loud voice, using profanity, screaming, shouting)
(c) Physical aggression (e.g. grabbing, shoving, pushing, resisting, hitting others, kicking objects or people, scratching, biting, throwing objects, hitting self, slamming doors, tearing things, and destroying property)
C. Behaviors are severe enough to produce excess disability, which in the clinician's opinion is beyond that due to the cognitive impairment and including at least one of the following:
(a) Significant impairment in interpersonal relationships
(b) Significant impairment in other aspects of social functioning
(c) Significant impairment in ability to perform or participate in daily living activities
D. While co-morbid conditions may be present, the agitation is not attributable solely to another psychiatric disorder, suboptimal care conditions, medical condition, or the physiological effects of a substance

Adapted from: Cummings J, Mintzer J, Brodaty H, Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. *Int Psychogeriatr* 2015; 27:7–17

Frontal-subcortical and cortico-cortical network dysfunction is proposed as of the basis for the agitation syndrome [8].

The symptom of agitation may be caused by pain or any other discomfort, medical comorbidities, environmental factors or drug effects. The optimal approach to treating agitation in AD requires assessing the medical circumstances with careful verification of medications. This step should be followed by thorough assessment of symptom severity, cognitive function, and co-occurrence of other NPS. Additionally individual vulnerability to adverse effects of pharmaceuticals should be considered.

Nonpharmacologic, behavioral interventions are crucial in the management of agitation in AD and are considered first-line treatments. Meta-analyses of various behavioral approaches found that behavior management therapies, care by specific types of caregiver in residential care, and staff education had the most lasting benefits. Music therapy and sensory stimulation had positive but only short-lived effects [39].

When psychosocial approaches are inadequate, antipsychotics, antidepressants, anticonvulsants, and other classes of drugs are utilized.

ChEIs studies provide only modest evidence to support benefit from their use in managing agitation [16]. In clinical practice, ChEIs are not helpful when immediate intervention is required [8]. A study comparing galantamine with risperidone, showed that the levels of agitation decreased in both treatment groups, but the improvement was significantly greater in the risperidone group [40].

Memantine provides modest benefit in the treatment of agitation and aggression in dementia and is well tolerated. In pooled, retrospective analyses of data from three placebo-controlled trials in moderate to severe AD, memantine showed significant reduction in agitation, as well as aggression or psychosis [32].

Atypical antipsychotics are commonly used off label despite modest clinical benefits, side-effect burden and risk of mortality. Atypical antipsychotic were more beneficial than placebo and were associated with decreases in caregiver burden but adverse effects limit their overall effectiveness [41].

There is some evidence to support the use of typical antipsychotics to manage aggression and agitation in the acute clinical setting. Haloperidol is useful in treatment of aggression with agitation [42]. The use of typical antipsychotics in NDD even in acute situations is considered high risk. Typical antipsychotics are not recommended in non-emergent treatment of agitation in dementia [43].

Experts recommend that risperidone, olanzapine and aripiprazole be used for severe agitation, aggression and psychosis associated with AD where there is risk of harm to the patient and/or others [13]. The potential benefit of all antipsychotics must be weighed against the significant risks, such as cerebrovascular adverse events and mortality.

A metaanalysis of four large placebo-controlled clinical trials supported risperidone's efficacy in the management of agitation and aggression even in severely impaired AD patients [35]. Risperidone may be considered as an option for short term intervention in cases of acute, treatment-resistant agitation in AD.

If there is no clinically significant response after a 4-week trial of an adequate dose of an antipsychotic drug, the medication should be tapered and withdrawn. In cases of adequate response an attempt to taper and withdraw the drug should be made within 4 months of initiation, unless the patient experienced a recurrence of symptoms with prior attempts at dose reduction.

There is modest evidence to support effectiveness of carbamazepine in targeting agitation and aggression in AD [16]. In practice, its use is limited by the risk of common side effects such as dizziness, sedation, ataxia, confusion, headaches, nausea, vomiting, diarrhea, blurred vision. More rare but significant adverse effects include inappropriate antidiuretic hormone with hyponatremia, cardiac and hepatotoxicity, and increased risk of suicidal behavior and ideation [4]. Patients should also be explicitly informed of warnings for aplastic anemia, agranulocytosis, and rare but sometimes fatal dermatologic adverse reactions.

The evidence for valproate in management of agitation in AD is mixed, with a meta-analysis of pooled results proving valproate ineffective and associated with unacceptable rates of adverse events (notably sedation and urinary tract infections) [13]. Among other pharmaceuticals from this category topiramate has some efficacy; gabapentin, lamotrigine, oxycarbamazepine and levetiracetam have been the subject of observational or uncontrolled studies and are considered as low priority agents.

Trazodone, a hypnotic and antidepressant (pharmacologically a serotonin antagonist and reuptake inhibitor), is used for management of irritability, agitation and aggression in AD. Trazodone has sedating properties with minimal anticholinergic activity. Trazodone has a favorable safety profile if administered in small doses and appears to produce a stabilization of the circadian rhythms in individuals with AD

[44]. A few retrospective or observational studies suggest that trazodone may be effective for the treatment of aggression or agitation in AD [45].

The most promising potential pharmacological alternatives to antipsychotics and anti-epileptic agents include citalopram, dextromethorphan/quinidine, and prazosin [46]. Comparator studies indicate that sertraline and citalopram are probably as effective as risperidone in treating agitation in dementia. A recent study had shown that dextromethorphan/quinidine significantly improved AD-associated agitation, reduced caregiver burden, and was generally well tolerated [47].

Depression of Parkinson's Disease

Depression, anxiety, psychosis, cognitive decline, and autonomic or sleep disturbances may be observed during the course of PD. Depression is common in PD, occurring in 40–50% of patients. Depression negatively impacts quality of life and worsens already impaired motor and cognitive abilities [48]. Depression of PD tends to be accompanied by cognitive impairment and emerges in advanced stages of the disease. Depression of PD frequently clusters with other NPSs; co-occurrence with anxiety is nearly universal reaching 92% [49]. PD has a broad range of severity from severe depression consistent with major depressive disorder to undifferentiated and even subclinical forms of depression. The mood disorder may have a fluctuating course in PD. In some cases depression is present only during the “off” period [48]. (Table 23.5) provides the diagnostic criteria for depression of PD [52].

Table 23.5 Criteria for depression of PD modified from DSM-IV criteria for major depression as recommended by NINDS/NIMH Work Group [52]

(a) Persistence and general pervasiveness of 5 or more of 9 potential symptoms during the same 2-week period that represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure that is present most of the day, nearly every day, as indicated by either subjective report or observation made by others.
1. Depressed mood
2. Markedly diminished pleasure from all, or almost all, activities
3. Loss or gain in weight or appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate, or indecisiveness
9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
(b) Symptoms do not meet criteria for a DSM mixed episode (presence of phenomena of both a manic and a depressed episode)
(c) Symptoms cause clinically significant distress or functional impairment
(d) Symptoms are not better accounted for by bereavement

Morphologic and functional neuroimaging studies demonstrate that depression in PD correlates with reduced activity of neural networks including prefrontal cortex, thalamus anterior and posterior cingulate structures. Degeneration of mesolimbic dopamine, norepinephrine, and serotonin pathways in orbital-frontal circuits and sub-cortical structures, such as the locus coeruleus, dorsal raphe nuclei, and ventral tegmental area, are thought to be associated with depressive symptoms in PD [50]. Functional neuroimaging studies implicate cortical cholinergic circuitry in dementia and depression of PD [51]. Depressive symptoms mainly: anhedonia, anergia, early morning awakening, and psychomotor retardation overlap with features of PD. Despite the overlap of symptomatology, a diagnosis of depression should be made if the core mood features of depression are present. Because of significant risk of under-detection, all PD patients should be screened periodically to detect depression. Additionally, because anxiety and depressive symptoms are frequently co-morbid in PD, a finding of anxiety should prompt screening for mood disorder [52].

Many studies demonstrate the efficacy of medications as well as psychotherapies for PD depression. Ideally in the management of PD depression pharmacological and nonpharmacologic intervention should be initiated concomitantly to promote optimal response.

Use of cognitive behavioral therapy (CBT) for depression and anxiety of PD is supported by strong evidence, including controlled trials [53]. The goal of CBT is to provide a structured approach that helps people to identify maladaptive thoughts contributing to emotional discomfort and to replace them with more enabling alternatives.

In terms of pharmacotherapy, experts recommend dopamine agonists (DA) as a first step in the management of depression of PD assuming it is compatible with the management of the motor symptoms of PD. Pramipexole (range of doses 0.3–4.2 mg/day) and ropinirole (10 mg/day) have antidepressant properties in patients with PD [54–56]. DAs use may be limited since this group of medication is linked to risk for developing impulse control disorders. Regular monitoring to capture symptoms like pathologic gambling, hypersexuality, and overspending in the course of DA therapy is crucial.

If an antidepressant agent is warranted, tricyclic antidepressants (TCAs) should be considered first (unless cognitive impairment is present). TCAs inhibit reuptake of dopamine, norepinephrine, and, to a lesser extent serotonin. TCAs also possess alpha-adrenergic antagonist, antimuscarinic, and antihistaminic properties. Almost all TCAs: amitriptyline, desipramine, imipramine, and nortriptyline (with the exception of doxepine) have been demonstrated to be potent antidepressants in randomized controlled trials involving patients with PD. The secondary amine TCAs (e.g., desipramine and nortriptyline) are preferred due to better tolerability and fewer anticholinergic effects. Desipramine and imipramine may improve motor symptoms of PD [49, 51]. In a subset of patients, such as those with hypersalivation or overactive bladder, the antimuscarinic activity of TCAs may be of additional benefit. Sedating TCAs may be helpful for the treatment of depression with insomnia.

In general, anticholinergic properties of TCAs limit their use in PD patients with existing or emerging cognitive dysfunction. Although infrequent, the TCAs also have the potential to induce cardiac conduction disturbances. If the use of a TCA is limited

due to cognitive impairment, comorbid medical conditions or treatment-emergent adverse effects, the SSRIs should be considered. SSRIs are well tolerated with the exception of tremor, which may be induced or worsened by SSRIs. Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline were similarly effective for the treatment of depression in PD. Among the SSRIs, citalopram and sertraline are preferred due to efficacy, tolerability, and low drug interaction potential. In addition to SSRIs and TCAs, several other antidepressants including bupropion, duloxetine, mirtazapine, moclobemide, nefazodone, and venlafaxine have been evaluated in controlled trials for the management of depression in PD. Both open label and placebo-controlled data demonstrate that duloxetine and venlafaxine are well tolerated and improve depressive symptoms in patients with PD. SNRI's however were found to have lower acceptability and tolerability than SSRIs in PD [57].

Nonselective monoamine oxidase (MAO) inhibitors (isocarboxazid, phenelzine, and tranylcypromine) should be avoided especially in levodopa-treated patients because of the risk of hypertensive crisis. The selective MAO-B inhibitors (selegiline) may be beneficial in the treatment of PD depression. MAO-B inhibitors should be however regarded as higher risk and low on the list of therapeutics for this indication.

Mirtazapine, a multiple-mechanism antidepressant (presynaptic alpha-2 antagonist blocker of 5-HT_{2a}, 5-HT_{2c}, 5-HT₃, and H-1 receptors) is a promising treatment option for depression of PD. Evidence suggests that mirtazapine may also improve tremor and levodopa-induced dyskinesias [58].

In cases where response is inadequate, switching to an agent from a different class (as opposed to augmentation) is recommended. Most antipsychotics are poorly tolerated in PD patients because of their antidopaminergic properties. Clozapine and quetiapine are exceptions and their use in complicated cases of mood disorders that accompany PD may be considered.

Use of mood stabilizers is limited by side effects: lithium requires very close monitoring and usually worsens motor symptoms in PD [48] and valproic acid is not routinely recommended since it is known to cause parkinsonism in the elderly and likely has a similar effect in those with PD [59].

ECT should be considered for patients with severe and treatment-resistant depression especially when complicated by psychosis or when the patient is at high risk for self-harm. ECT is a safe and effective modality in the treatment of depression in PD (Fig. 23.4).

Psychosis of Parkinson's Disease

Psychosis is debilitating symptom of PD, it is an independent risk factor for nursing home placement, and, increases caregiver distress and patient mortality [51].

Visual hallucinations are the most common psychotic manifestation in PD. Auditory, olfactory, tactile and gustatory hallucinations are infrequently found and usually coexist with visual ones. Minor hallucinations such as presence and

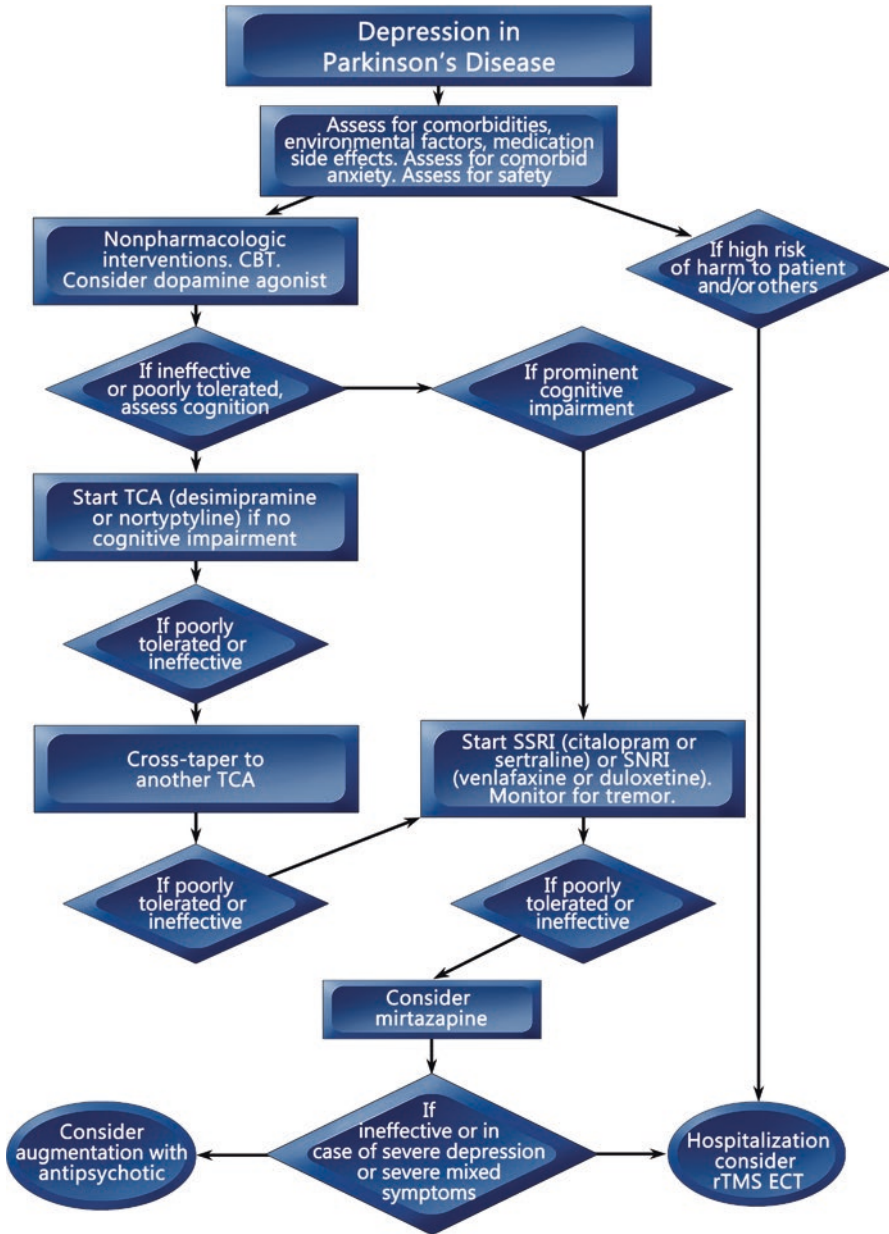


Fig. 23.4 Treatment of depression in Parkinson's disease

passage hallucinations may precede structured visual hallucinations. Delusions occur in about 5% of PD patients Dopaminergic medications, cognitive dysfunction, depression, sleep disturbances, and longer duration of PD are risk factors for the emergence of psychosis in PD [60]. (Table 23.6) provides the criteria for psychosis of PD [66].

Table 23.6 Proposed diagnostic criteria for PD associated psychosis [66]

(a)	Characteristic symptoms
	Presence of at least one of the following symptoms (specify which of the symptoms fulfill the criteria):
	1. Illusions
	2. False sense of presence
	3. Hallucinations
	4. Delusions
(b)	Primary diagnosis
	UK brain bank criteria for PD
(c)	Chronology of the onset of symptoms of psychosis
	The symptoms in Criterion A occur after the onset of PD
(d)	Duration
	The symptom(s) in Criterion A are recurrent or continuous for 1 month
(e)	Exclusion of other causes
	The symptoms in Criterion A are not better accounted for by another cause of Parkinsonism such as dementia with Lewy bodies, psychiatric disorders such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features, or a general medical condition including delirium
(f)	Associated features: (specify if associated)
	With/without insight
	With/without dementia
	With/without treatment for PD (specify drug, surgical, other)

The pathophysiology of psychosis in PD is most likely multifactorial with disruption of serotonin, dopaminergic, and acetylcholine systems [61]. Neuropathological studies link the development of psychosis with progressive formation of Lewy bodies in cortex, amygdala, hippocampus [62].

The only agent with FDA approval for treatment of PD psychosis is pimavanserin a selective-serotonin inverse agonist that preferentially targets 5-HT_{2A} receptors, while avoiding activity at dopamine and other receptors commonly targeted by antipsychotics. Pimavanserin was shown to be effective in a trial in which adults with PD psychosis were randomly assigned to take 40 mg of pimavanserin or placebo daily for 6 weeks. Patients taking pimavanserin experienced fewer and less severe hallucinations and delusions without worsening the primary motor symptoms of PD. The most common adverse effects reported by patients taking pimavanserin included peripheral edema, nausea, and confusion [10] (Fig. 23.5).

Efforts to treat psychosis of PD with antipsychotics commonly used for primary psychotic disorders to date have been futile and associated with significant deterioration of the motor symptoms [63]. Typical antipsychotics, especially potent blockers of dopaminergic receptors are in general contraindicated in PD. Novel, atypical antipsychotics although safer seem to be of limited efficacy in managing symptoms of PD.

Risperidone has been to some extent beneficial in managing psychotic symptoms of PD Dementia (PDD). Treatment with risperidone improved levels of social, occupational, and psychological functioning [64]. In practice however worsening of parkinsonism limits use of this agent.

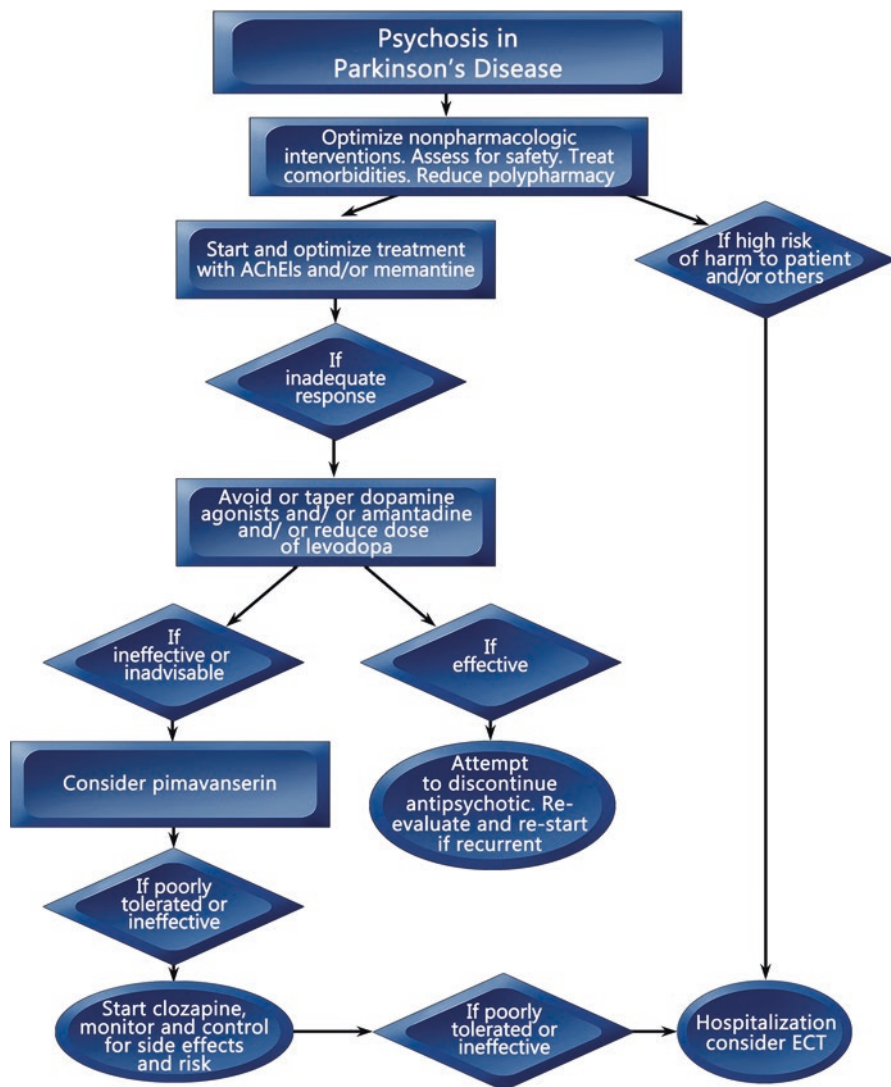


Fig. 23.5 Treatment of psychosis in Parkinson's disease

Clozapine is efficacious in the treatment of PD psychosis in randomized controlled trials even in very small doses (6.25–50 mg daily) [63, 65]. The risk of agranulocytosis and the necessity of blood monitoring with clozapine leads to choice of other antipsychotics, mainly quetiapine (12.5–150 mg) before attempting use of clozapine [63]. Quetiapine is the most frequently prescribed antipsychotic to target psychotic symptoms in PD. Firm conclusions about its efficacy cannot be drawn. Studies show that patients taking quetiapine experienced fewer side effects than reported with other antipsychotics, but it has yet to be proven to be more effective than placebo in the treatment of psychosis in this population.

In severe cases hospitalization should be considered. Somatic therapies may be an option in such a cases as well. In PD, ECT was proved to be effective not only for depression and motor symptoms but for psychosis. It might be considered to treat psychosis that has not responded to other interventions [51].

ICD-10 Codes

G30 Alzheimer's disease

G30.0 Alzheimer's disease with early onset

G30.1 Alzheimer's disease with late onset

G30.8 Other Alzheimer's disease

G30.9 Alzheimer's disease, unspecified

or

G30.9 Major neurocognitive disorder due to probable or possible Alzheimer's disease

Additional codes

F02.80 without behavioral disturbance,

F02.81 with behavioral disturbance

F06.31 Depressive disorder due to Alzheimer's disease with depressive features,

F06.32 Depressive disorder due to Alzheimer's disease with major depressive-like episode

F06.34 Depressive disorder due to Alzheimer's disease with mixed features

G20 Parkinson's disease

Additional codes

F06.2 Psychotic Disorder Due to Parkinson's disease with delusions

F06.0 Psychotic Disorder Due to Parkinson's disease with hallucinations

F06.31 Depressive disorder due to Parkinson's disease with depressive features,

F06.32 Depressive disorder due to Parkinson's disease with major depressive-like episode

F06.34 Depressive disorder due to Parkinson's disease with mixed features

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Chapter 24

Pseudobulbar Affect

Jeffrey Cummings

Clinical Pearls

- In pseudobulbar affect, the expressed emotion is at variance with, or greatly exaggerated from, the emotional trigger
- Patients with pseudobulbar affect often have evidence of pseudobulbar palsy on neurological examination
- Pseudobulbar affect can be distinguished from depression with crying based on features of the associated mood disorder in patients with depression

Introduction

Pseudobulbar affect (PBA) refers to involuntary and inappropriate laughing and/or crying occurring in the context of a neurological disease. The emotional expression is at variance with the felt emotion of the individual (e.g., laughing when one feels sad) or is greatly disproportionate to the stimulus (e.g., laughing uproariously in a situation with limited humor). The episodes are typically 1–2 min in duration and may occur many times per day. The affective contortions of the face sometimes make it difficult to distinguish between laughing and crying. PBA occurs in a diverse array of circumstances (listed below); it diminishes the quality of life of the individual and the quality of the social relationships in which the individual can engage.

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Diagnostic Criteria

Table 24.1 provides the diagnostic criteria for PBA.

PBA occurs in many neurological disorders and Table 24.2 provides the differential diagnosis to be considered for the patient presenting with PBA.

PBA must be distinguished from depression, especially where the major manifestation of the PBA is crying. Table 24.3 shows distinguishing features of PBA and depression.

Assessment

PBA reflects the loss of supranuclear control of subcortical affective motor programs and is seen typically in conjunction with lesions of the descending pyramidal tracts. Cerebellar lesions have also been associated with the syndrome.

Table 24.1 Diagnostic criteria for PBA (adapted from Cummings et al. [1]; in this reference PBA was labeled involuntary emotional expression disorder [IEED])

Necessary elements

Episodes of involuntary or exaggerated emotional expression that result from a brain disorder; including episodes of laughing, crying, or related emotional displays

- Episodes represent a change from the person's usual emotional reactivity
 - Episodes may be incongruent with the person's mood or in excess of the corresponding mood state
 - Episodes are independent or in excess of any provoking stimulus
-

The disturbance causes clinically significant distress or impairment in social or occupational functioning

The symptoms are not better accounted for by another neurologic or psychiatric disorder (e.g., gelastic or dacrystic epilepsy, facial dystonia, facial or vocal tics, facial dyskinesias, mania, depression, panic disorder, psychosis)

The symptoms are not the direct physiological effect of a substance (e.g., drug of abuse or medication)

Supportive observations

Autonomic changes (e.g., flushing of face)

Pseudobulbar palsy signs (e.g., increased jaw jerk, exaggerated gag reflex, tongue weakness, dysarthria, dysphagia)

Proneness to anger or episodes of anger

Descriptive characteristics

Episodes are sudden in onset

Episodes typically are brief (seconds to minutes)

Episodes vary in severity among patients (each episode is of similar severity within individual patients)

Episodes are stereotyped. Stereotypical features include not only the appearance of episodes across disorders, but also within patients. Stereotyped attributes can include frequency, length, and types of episodes

Table 24.2 Differential diagnosis of causes of PBA (major causes)

Alzheimer’s disease (AD)
Amyotrophic lateral sclerosis (ALS)
Brain tumors
Frontotemporal dementia, especially the forms with motor neuron disease
Multiple sclerosis (MS)
Neurosyphilis
Normal pressure hydrocephalus
Parkinson’s disease (PD)
Progressive supranuclear palsy
Stroke, especially bi-hemispheric infarctions
Traumatic brain injury
Vascular dementia
Wilson’s disease

Table 24.3 Features distinguishing depression from PBA with crying

Feature	Depression	PBA with crying
Mood	Underlying mood state of sadness, helplessness, hopelessness, worthlessness, and suicidality/ thoughts of death	Affect (crying) disproportionate to underlying mood; sadness may or may not be present, anger and frustration commonly accompany the episodes
Duration	Tearful for prolonged periods	Brief (1–2 min) stereotyped episodes
Associated neurological disease	None necessary	Obligatory relationship with a neurological illness
Pseudobulbar palsy on neurological examination	Absent unless depression occurs with neurological disorder	Present to some degree
Emotional expression	Crying, tearfulness	Crying, laughing, or both
Emotional experience	Mood congruent with sadness	Independent of the expressed emotion or excessive
Voluntary control	Often can be modulated by the situation	None to minimal
Stereotypy	Crying episodes are variable	Episodes are stereotyped
Provocative stimulus	Crying may be provoked by specific mood-related situations	Usually specific to each patient and may be minimal compared to the emotional response; in some cases no provocation is apparent
Fatigue	Common	No relationship
Changes in appetite	Anorexia common	No relationship
Sleep disorder	May be present	No relationship
Diurnal variation	May be present	Not present
Anhedonia	Common	Not present

PBA typically occurs as part of a limited or extended pseudobulbar palsy syndrome with evidence of bilateral pyramidal tract disease. On neurological examination, the findings of pseudobulbar palsy may include:

- Bilateral facial weakness for voluntary expression with intact involuntary affective expression
- Dysarthria
- Dysphagia
- Brisk jaw jerk
- Brisk facial muscle reflexes
- Prominent gag reflex
- Upper motor neuron signs in the limbs
 - Brisk limb reflexes
 - Babinski signs
 - Limb spasticity

The neurological examination will be directed at identifying the underlying neurological disorder—multiple sclerosis, amyotrophic lateral sclerosis, stroke, traumatic brain injury, etc. Brain imaging often reveals evidence of brain disease affecting the pyramidal tracts bilaterally.

PBA can be assessed with the Pathological Laughing and Crying Scale (PLACS) [2] or the Center for Neurological Science Liability Scale (CNS LS) [3].

Treatment

Dextromethorphan/quinidine (DM/Q; Nuedexta™) is the only currently approved treatment for PBA [4]. Treatment is initiated at one tablet daily for 1 week and is then titrated upward to one tablet twice daily. Treatments typically produce a greater than 50% reduction of PBA episodes. Side effects to be monitored include falls, dizziness, and lethargy. In some cases, PBA may improve with treatment with antidepressants, including selective serotonin reuptake inhibitors or tricyclic antidepressants (i.e., nortriptyline) [2]. When PBA resides, periodic attempts to reduce or eliminate treatment should be made (Fig. 24.1).

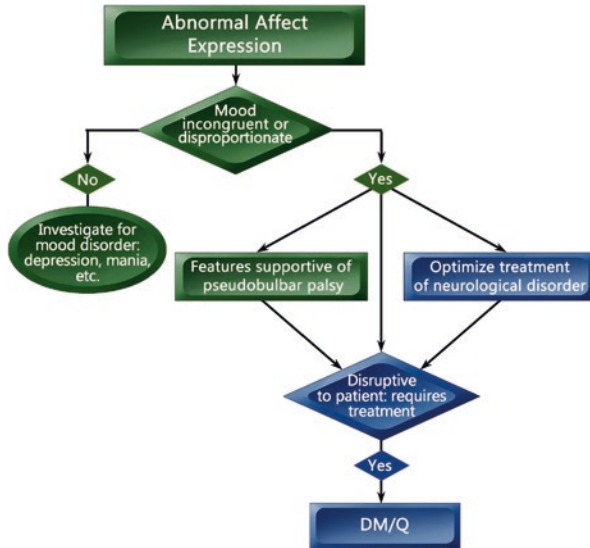


Fig. 24.1 Assessment and management of PBA

ICD-10 Codes

Emotional lability R45.86

Disclosures Dr. Cummings has provided consultation to Abbvie, Acadia, Accera, Actinogen, ADAMAS, Alkahest, Alzheon, Anavex, Astellas, Astra Zeneca, Avanir, Axovant, Biogen-Idec, Biotie, Boehinger-Ingelheim, Chase, Eisai, Forum, GE Healthcare, Genentech, Grifols, Intracellular Therapies, IRIS, Ionis Pharmaceuticals, Lilly, Lundbeck, MedAvante, Merck, Neurotrope, Novartis, Nutricia, Otsuka, Pfizer, Probiodrug, QR Pharma, Resverlogix, Roche, Servier, Sunovion, Suven, Takeda, Toyoma, Transition Therapeutics, and United Neuroscience companies.

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