Prognosis of Neurological Diseases

Angelo Sghirlanzoni
Giuseppe Lauria
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Editors

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Foreword

Clinical neurology has dramatically changed in the last years, mainly because of developments in new diagnostic tools and innovative disease-modifying therapies. Recently improved imaging and biomolecular techniques allow for more accurate diagnosis of many neurological disorders and, in some cases, for early and/or preclinical diagnosis, based on biomarkers, even before clinical manifestations. Moreover, new therapies are available for selected neurological disorders and have changed the natural history of these diseases.

Based on these premises, the prognosis of most neurological disorders has changed in recent years, with wide implications for patients, their families and for the disease burden.

Most textbooks of clinical neurology do not adequately focus on this aspect, although in everyday clinical practice, and especially when neurologists speak with patients and their relatives, they must repeatedly address questions regarding prognosis. Indeed, the outcome of a disease is *the* clinical question with the highest priority for both clinicians and patients.

Prognosis of Neurological Diseases is based on a completely new perspective and aims to fill this gap in neurological literature.

It covers the full range of disorders of the central and the peripheral nervous system, recapitulating the main clinical issues concerning differential diagnosis while utilising the help of new imaging and biomolecular techniques in order to provide very accurate prognostic estimates.

Key facts, such as clinical issues, top differential diagnosis and laboratory and imaging biomarkers, are highlighted at the beginning of each chapter. Focus is then devoted to available therapies, including the most recent trials, and then prognosis is extensively discussed in relation to natural history, accurate diagnosis and available therapies. Selected references, including the most important trials and meta-analyses, are provided at the end of each chapter. These are useful for readers who wish to study a particular problem further.

I believe that this book will be particularly helpful as a practical guide when discussing prognosis with patients and their families in the clinical ward. It will also help develop realistic expectations of the effect of medical interventions and thus foster a true patient-doctor alliance.

Moreover, the book is designed to provide doctors, lawyers and other professionals with an understanding of the issues that need to be considered when an estimate of prognosis and life expectancy is the subject of a legal decision or legal dispute.

The authors and editors stand among the leading experts in their various fields and guarantee accurate and updated information on the topics covered, with a critical appraisal and personal views on each subject. I fully endorse this book and suggest it as a valuable companion for clinical neurologists.

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Preface

Michelangelo Merisi (Caravaggio) – La buona ventura (Gypsy Fortune-Teller) *1594*. Pinacoteca Capitolina, Rome. Reprinted with permission.

In Caravaggio's picture, an enchanted young man gazes into the face of a lovely gypsy while she caresses his hand and slips the ring off his finger.

This is not an anecdote of two specific people but may be an everyday tale.

In the same way, just as luck seems to tap our shoulder, we can lose our most precious gifts, our health or even our life.

There is no longer any need to have our hand read to guess about our diseases for we have evidence-based foresight, namely, prevention when we are healthy and prognosis when we are ill.

Prognosis is often not specifically addressed. Even in specialist teaching academies, emphasis is usually on pathogenesis or molecular genetics and, obviously, therapy; perhaps, there is a sort of hesitation in considering prognosis a scientific procedure and not a shamanic art. Thus, this crucial topic remains relatively neglected in clinical neurology. We hope our volume will contribute to fill the gap.

Milano, Italy The Editors

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Vascular Disease: Ischemic Stroke

1

Anna Bersano, Luigi Caputi,
and Eugenio Agostino Parati

Key Facts

- **Clinical features**
  - **Definitions** – Stroke: sudden onset focal neurological deficit lasting >24 h. *TIA:* brief neurological deficit lasting >24 h.
  - **Demographics** – Stroke incidence ranges from 240 to 600 per 100,000 people.
  - **Risk factors** – Hypertension, diabetes, lipids, cardiac diseases, smoke, obesity, etc.
  - **Diagnostic markers** – Abrupt onset of a clearly focal neurological deficit localized to a specific vascular territory backed up by neuroimaging.
    - **Blood** – To reveal predisposing causes (i.e., polycythemia, sickle cell disease, renal impairment, electrolyte disturbances, hyper/hypoglycemia).
    - **Cerebrospinal fluid** – To exclude inflammatory, dysimmune, neoplastic syndromes.
    - **Genetics** – Monogenic disorders account for 1–5 % of stroke. Most strokes are believed to be polygenic.
- **Imaging**
  - **Cerebral CT scan** – Frequently normal after ischemic stroke but may show subtle changes.
  - **Cerebral MRI** – Is the investigation of choice; DWI sequences demonstrate acute lesions in the first few hours after stroke.
  - **Arterial imaging/carotid Doppler ultrasonography**, **computed tomography angiography (CTA), or magnetic resonance angiography (MRA)** provide information about vessels status.
- **Top differential diagnoses**
  - Epileptic seizures, toxic/metabolic disorders, syncope, subdural hematoma, peripheral vestibulopathy.
- **Prognosis**
  - About a quarter of stroke patients die within a month, about a third by 6 months, and a half by 1 year.

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Abbreviations

ASA, anterior spinal arteries; CADASIL, autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CAS, carotid artery stenting; CCS, Causative Classification of Stroke; CEA, carotid endoarteriectomy; CT, computed tomography; CSF, cerebrospinal fluid; CTA, computed tomography angiography; DALYs, Disabilty Adjusted Life Years; LACI, lacunar infarcts; MRA, magnetic resonance angiography; mRS, modified Rankin Score; OCSP, Oxfordshire Community Stroke Project; PACI, partial anterior circulation infarcts; POCI, posterior circulation infarcts; PSA, posterior spinal arteries; RCT, randomized controlled trial; SU, stroke unit; TACI, total anterior circulation infarct; TOAST, acute stroke treatment; ET, endovascular treatment

1.1 Stroke and TIA

1.1.1 Definitions

Stroke is the sudden onset of a focal neurological deficit lasting more than 24 h in which non-vascular causes have been excluded.
Transient ischemic attack (TIA) is a brief neurological deficit of vascular origin lasting less than 24 h, often less than 1 h. With the worldwide use of neuroimaging, TIAs are now classified as transient neurologic events without signs of acute infarction on imaging [1].

1.1.2 Epidemiology

Stroke causes about 9 % of death around the world and it is the second most common cause of death and the third most common cause of disability-adjusted life years (DALYs) [2]. The worldwide incidence and prevalence of stroke are 9.0 and 30.7 million, respectively, with a higher incidence in the Eastern Pacific, Europe, and Southeast Asia. Due to advances in Western healthcare, the prevalence of stroke since 1970 has decreased by 42 %, whereas it has more than doubled in low-income to middle-income countries [3].

1.1.3 Associated Risk Factors

Common risk factors, which can be classified in modifiable or not [4] (Table 1.1), explain only about 60 % of the attributable risk. Investigation is needed to identify the risk factors that account for the 40 % gap, some of which might be genetic [5].

1.1.4 Subtypes and Pathogenesis

The most commonly used classifications of ischemic stroke are based on the presumed mechanism of the focal brain injury, and the type and localization of the vascular lesion. The most commonly used etiopathological classification is *TOAST criteria*, which categorizes stroke in: (a) large-artery atherosclerotic infarction; (b) embolism from a cardiac source; (c) small-vessel disease; (d) other determined cause (such as dissection, hypercoagulable states, or sickle cell disease); and (e) infarcts of undetermined cause. However, the difficulties in classifying stroke with multiple etiologies led to the development of new classification systems, such as web/evidence-based decision-making. However, among classification systems, the *Oxfordshire Community Stroke Project (OCSP),* although less used, categorizes stroke syndromes into total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), lacunar infarcts (LACI), and posterior circulation infarcts (POCI), and has been estimated to better predict the prognosis (higher mortality in TACI group, high recurrence in PACI group).

1.1.5 Diagnostic Markers

The diagnosis of stroke/TIA requires a compatible history (an abrupt onset of a clearly focal

Table 1.1 Risk factors of stroke

Modifiable risk factors
Hypertension
Diabetes
Lipids
Cardiac disease (including atrial fibrillation, recent large myocardial infarction, mitral stenosis)
Infective endocarditis
Cigarette smoking
Obesity
Metabolic syndrome
Alcohol consumption
Physical inactivity
Sickle cell disease
Hyperhomocysteinemia
Use of oral contraceptives
Use of illicit drugs
Migraine
Unmodifiable risk factors
Age
Gender
Genetic risk factors
Race/ethnicity
Geographic location

neurological deficit) and neurological examination (a neurological deficit that can be localized to a specific vascular territory) backed up by neuroimaging excluding mimics.

1.1.5.1 Blood

May reveal predisposing causes, such as polycythemia, sickle cell disease, renal impairment, electrolyte disturbances, and hyper-/hypoglycemia as well as other risk conditions such as hyperlipidemia, hyperhomocysteinemia, or concomitant infections that should be treated since they impair brief-term and long-term prognosis.

1.1.5.2 CSF

Cerebrospinal fluid examination is indicated in some patients for two main reasons:

1. To exclude other diagnosis such as inflammatory and dysimmune conditions, infections or malignancies
2. To evaluate new prognostic markers (i.e., orexin A, bradykinin levels)

1.1.5.3 Genetics

Evidence from epidemiological studies in twins, families, and animal models supports the role of genetic factors in stroke pathogenesis and suggests that these factors play a major role in younger age groups and in certain stroke subtypes [6].

Monogenic disorders, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); Fabry disease; cerebral autosomal recessive A arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL); hereditary cerebral amyloid angiopathy (H-CAA); hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS); mitochondrial encephalopathy with lactic acidosis and stroke like episodes (MELAS); and, more recently, COL4A1 syndromes are well-recognized causes of stroke and small-vessel disease. In addition, some inheritable connective disorders have been associated with stroke, particularly with cardioembolic subtype and with stroke caused by epiaortic vessel dissections. Disease progression and long-term prognosis as well as causes of death in these patients are largely unknown. Only one study reported outcome data for CADASIL. The median ages of onset for inability to walk without assistance, bedridness, and death were significantly lower in men than in women (58.9 vs. 62.1; 62.1 vs. 66.5; and 64 vs. 70.7 years, respectively) (all $P \leq 0.01$) [7].

However, monogenic diseases explain less than 5 % of all stroke cases. In most cases, stroke is a polygenic disorder for which classic patterns of inheritance cannot be identified [8].

1.1.6 Imaging and Other Investigations

- *Cerebral CT* scan is frequently normal after ischemic stroke.
- *Cerebral MRI* is the investigation of choice in acute ischemic stroke. DWI sequences demonstrate acute lesions in the first few hours after stroke and are much more sensitive than CT scan (Fig. 1.1).
- Arterial imaging with carotid Doppler ultrasonography, computed tomography angiography

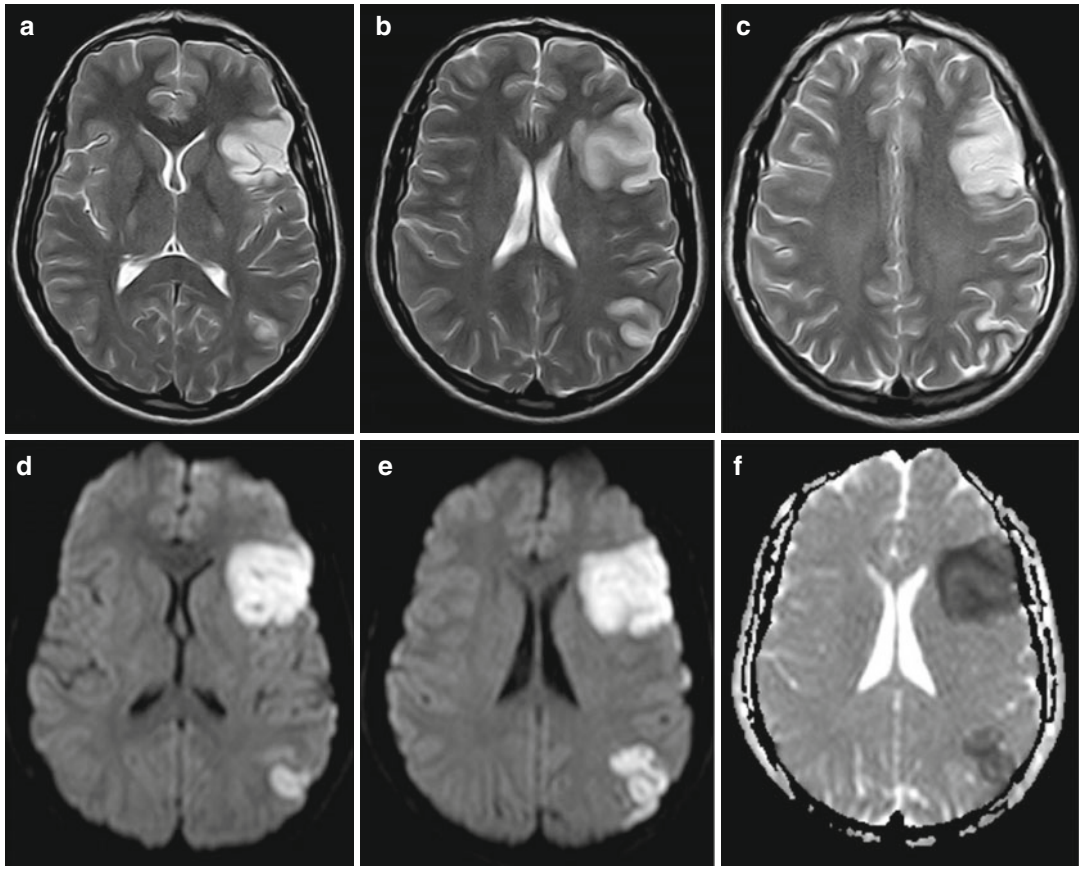

Fig. 1.1 Acute ischemic stroke. Axial T2-weighted images, (**a**–**c**), demonstrate cortical-subcortical hyperintesities in the left frontal-opercolar and in the left temporal-parietal carrefour regions, "enhanced" in DWI images, (**d**, **e**), and in ADC map, (**f**)

(CTA), or magnetic resonance angiography (MRA) provide information about the status of intracranial and epiaortic vessels

- *Electrocardiography* is used to detect paroxysmal atrial fibrillation or cardiac ischemic acute disease.
- *Transthoracic or transesophageal* echocardiography is used to detect cardiac sources of embolism other than atrial fibrillation.

1.1.7 Top Differential Diagnoses

Epileptic seizures, toxic/metabolic disorders, syncope/pre-syncope, peripheral vestibulopathy, sepsis including meningoecephalitis, space-occupying lesions/hematoma, multiple sclerosis, migraine/familial hemiplegic migraine.

1.1.8 Principles of Treatment

1.1.8.1 Acute Phase Treatment

Stroke Units (SUs) The most substantial advance in stroke therapy has been the routine management of patients in stroke units (SUs), with stroke-dedicated beds and staff. SU treatment is effective in reducing mortality and disability in about 20 % of patients, independently from age, stroke subtype, and severity. Although the precise components of SU management responsible for the effectiveness of SUs are

unclear, monitoring, early mobilization, and general adherence to best practice could improve stroke outcome [9].

Thrombolysis (Recombinant tPA) Recombinant tPA (rtPA) is the only evidence-based effective therapy for acute ischemic stroke. The major adverse effect of thrombolysis is symptomatic intracerebral hemorrhage, seen in about 6–7 % of cases, but which is even lower in the European (SITS MOST) study population. Although the publication data of ECASS III study widened the therapeutic time window from 3 to 4.5 h, the number of patients who could receive rtPA treatment is small. However, substantial uncertainties about the efficacy in reducing death and improving functional outcome still remain regarding the longest time window, the efficacy in people older than 80 years, and the role of other potential influencing factors (i.e., stroke subtype, use of antiplatelet before stroke). A recent meta-analysis on 7012 patients seems to support the treatment efficacy independently of age or stroke severity and in at least a part of patients treated within 6 h [10].

Endovascular Treatment (ET) The available evidence from trials performed with different methodological approaches, including "bridging" and different devices, does not show that endovascular therapy achieves superior outcomes in comparison to intravenous thrombolysis for the acute treatment of ischemic stroke patients [11].

Decompressive Surgery for Ischemic Stroke Decompressive surgery, removal of part of the skull and duraplasty, has been proposed as a way to control raised intracranial pressure and reduce shifts of swollen brain tissue after stroke. The results of randomized trials show that decompression reduces death rate (ARR 38 %, 15–60; $p = 0.002$) and slightly improves the functional outcome, defined as an mRS score of 5 or 6 (mRS: 4 moderately severe disability; mRS 5: severe disability) in patients with space-occupying hemispheric infarction treated within 48 h of stroke onset. Seventy-eight percent of survival was observed in patients submitted to decompressive surgery versus 29 % of the medically treated. The modified Rankin Score (mRS) was ≤4 in 75 % of patients in the surgery group versus 24 % in controls; mRS was ≤3 in 43 % versus 21 % in the surgically and conservatively treated group, respectively [12]. There is no evidence that this operation improves functional outcome when it is delayed for up to 96 h after stroke onset. Recent guidelines support the use of decompressive craniotomy in patients with swelling stroke who continue to deteriorate neurologically. Patients older than 60 years also benefit from this treatment [13]. The 3-year follow-up data of HAMLET study, which is the largest randomized trial in this field [14, 15], reported that surgical patients had a lower case fatality rate than controls, whereas the risk of a poor outcome did not differ between groups.

Hypothermia Pharmacological and physical cooling studies do not reduce the risk of death or dependency (OR 0.9; 95 % CI, 0.6–1.4) in patients with acute stroke [16].

1.1.9 Secondary Prevention of Stroke

1.1.9.1 Oral Antiplatelet Drugs

The overall use of antiplatelet agents in secondary prevention trials has been shown to provide about 22 % of relative risk reduction of stroke recurrence.

A recent meta-analysis, including 8 trials and 41,483 patients, showed that aspirin therapy at 160–300 mg daily, started within 48 h after ischemic stroke onset, reduces the risk of early recurrent ischemic stroke (OR 0.77; 95 % CI 0.69, 0.87) without a major risk of early hemorrhagic complications. However, clinical and laboratory evidence demonstrates diminished or no response to ASA in some patients, who labeled ASA resistance.

Currently, for patients with non-cardioembolic ischemic stroke or TIA, monotherapy with clopidogrel of 75 mg is considered an acceptable

option to reduce risk of recurrent stroke and other cardiovascular events (Class IIa; Level of Evidence B) [17].

In addition, the combination of aspirin plus extended-release dipyridamole has been found to be safe and effective in preventing disability (ESPRIT study).

However, the use of aspirin plus dypiridamole did not show different efficacy from clopidogrel alone, whereas the association between aspirin and clopidogrel compared to clopidogrel or aspirin in monotherapy is linked to an increased risk of hemorrhagic complications (MATCH study).

1.1.9.2 Anticoagulants

Evidence does not support the use of anticoagulation therapy in prevention of non-cardioembolic stroke, given the scarce benefit in reducing early recurrent ischemic stroke and the significant increase in symptomatic intracranial hemorrhages.

Indeed, anticoagulation has been demonstrated to be more effective than aspirin or aspirin plus clopidogrel in reducing the risk of recurrent stroke in patients with atrial fibrillation by about 70 % (hazard ratio 0.34, 95 % CI 0.20–0.57) with a relative small risk of major bleeding (ICH) (0.3–0.6 % per year) [18]. However, the increased risk of symptomatic intracranial hemorrhage in the early stroke phase limits the administration of these drugs within 48 h of stroke. Recently, new anticoagulant drugs, such as dabigatran, rivaroxiban, and apixaban, which do not require periodic monitoring and show similar efficacy and similar or reduced bleeding risks, are replacing warfarin therapy.

1.1.9.3 Lipid Lowering

Statins are effective in reducing stroke risk by 18 % in primary stroke prevention and 28 % in secondary stroke prevention (without increasing the risk of cerebral bleeding) [19]. The benefits appear to be greatest in patients with the highest reductions in LDL levels (50 % or more) and no cardioembolic strokes.

1.1.9.4 Revascularization

Carotid endoarterectomy (CEA) is the best medical therapy for secondary prevention in patients with recently symptomatic carotid stenosis ranging from 70 to 99 % and 50–69 %. CEA reduces the risk of stroke or death at 5 years, respectively, by 50 and 25 %, an outcome which should be balanced with the 5 % surgical risk of stroke or death from carotid endoarterectomy. In particular patients of male sex and older patients, carrying ulcerated carotid plaques and recently symptomatic stenosis (within 2 weeks from stroke) benefit from intervention. Carotid artery stenting (CAS) is associated with a lower risk of local hematoma, cranial nerve injury, myocardial infarction but with an increased risk of periprocedural stroke or death and with a long-term risk of carotid restenosis [20, 21]. In asymptomatic subjects, no clear recommendations are available: the only three published RCTs showed that CEA reduced the risk for ipsilateral stroke compared with medical therapy alone, whereas no RCT compared CAS versus medical therapy [22].

1.1.9.5 Blood Pressure Lowering

Gradual lowering of blood pressure reduces the risk of further stroke and myocardial infarction in all stroke patients although particular care is necessary in patients with epiaortic vessel stenosis or occlusions. There are no definitive data about the most effective class of antihypertensive drugs, the extent of lowering, and the ideal time to start blood lowering. It is believed that treatment has to be individualized based on patients' comorbidities [23].

1.1.9.6 Patent Foramen Ovale

Patients with cryptogenic ischemic stroke or TIA and a patent foramen ovale have a similar rate of recurrent ischemic stroke (1.6 % per year, 95 % CI 1.1–2.1 %) as patients without a patent foramen ovale (RR 1.1, 95 % CI 0.8–1.5). The additional presence of atrial septal aneurysm increases the risk of stroke (HR for both patent foramen ovale and atrial septal aneurysm vs. neither = 4.2; 95 % CI 1.5–12). However, patent foramen ovale closure was not associated with a significant reduction in stroke recurrence, whereas it was associated with a significant increase in new-onset atrial fibrillation (3.8 % closure vs. 1.0 % medical; RR 3.5, 95 % CI 1.5–8.3) [24].

1.1.10 Prognosis

About a quarter of stroke patients die within a month, about a third by 6 months, and a half by 1 year [25]. The major cause of early mortality is neurological deterioration with contributions from other causes such as infections, whereas after 6 months to 1 year, deaths are more commonly caused by cardiac disease. The 1-year mortality for patients with total anterior circulation syndromes (about 60 %) is higher than that of patients with partial anterior circulation and posterior circulation syndromes (about 15–20 %), which in turn is higher than in patients with lacunar syndromes (10 %).

A particularly poor prognosis is related to the so-called malignant middle cerebral artery syndrome (MCA) which is a clinical syndrome characterized by a rapid neurological deterioration due to edema from MCA stroke. In this condition, if not directed to decompressive surgery, about 80 % of patients die, usually for transtentorial herniation and brainstem compression, and most survivors are left severely disabled [14].

Acute ischemic stroke also produces severe dependency after 4 weeks in approximately one-third of hospitalized patients.

The best predictors of stroke recovery at 3 months are the initial severity of neurological deficit and older age (>65 years); other factors include high blood glucose concentrations, increased body temperature, and previous stroke. The risk of a recurrent stroke is highest early after an ischemic stroke or transient ischemic attack (TIA) – about 1 % at 6 h, 2 % at 12 h, 3 % at 2 days, 5 % at 7 days, and 10 % at 14 days. Therefore, ischemic stroke or TIA is a medical emergency that demands immediate diagnosis and treatment [26].

1.1.10.1 Early Recurrent Stroke

Patients at very high risk (>30 %) of recurrence within 7 days can be identified on the basis of "ABCD" score: (1) age, (2) blood pressure, (3) and clinical features, such as sudden onset, unilateral motor deficit, and speech disturbance lasting for longer than 10 min. All these factors predict a high risk of stroke soon after TIA, probably because they distinguish TIA from TIA mimics that have a more benign prognosis [26, 27].

Its updated versions, ABCD2 and ABCD3–I scores, have also been proposed to better identify a prognostic index predicting those patients at greatest risk who might benefit most from early risk-factor modification [27, 28].

1.1.10.2 Long-Term Recurrent Stroke Risk

The risk of recurrent stroke in survivors of acute stroke is about 11.1 % (95 % CI 9.0–13.3) at 1 year, 26.4 % (20.1–32.8) at 5 years, and 39.2 % (27.2–51.2) at 10 years [25]. In young adults (18–50 years of age) who have had a stroke, the 20-year risk of recurrent ischemic stroke is about 19 % (95 % CI 15–24). Vascular risk factors, previous symptomatic vascular disease (including stroke, myocardial infarction, or peripheral arterial disease), unstable vascular disease (recurrent recent ischemic events of the brain), embolic sources and causes (atrial fibrillation, embolism from the heart or large arteries), and cerebral microbleeds are considered as possible predictors of stroke recurrence at long-term follow-up.

1.2 Spinal Cord Infarction

Spinal cord infarction is rare and accounts for 0.3–1 % of all strokes. Since the arterial supply arises from the anterior and posterior spinal arteries (ASA and PSA, respectively), in addition to the perforating arteries and the long circumferential artery, the mechanisms underlying medullary infarctions may be distinct from infarctions in other areas. About 60 % of the spinal cord infarctions occurred perioperatively or were caused by aortic aneurysm or dissection.

Causes of ASA territory medullary infarction are resumed in Table 1.2.

Metameric 5 cervical and 4 and 5 dorsal levels are the higher susceptibility levels.

Young age, male sex, hypertension, and cervical stroke location were associated with severe neurological deficit at acute phase, whereas high serum glucose on admission was associated with poor improvement in the early phase.

Table 1.2 Causes of arterial spinal artery infarction

Hemodynamic	Cardiac failure, traumatic aorta rupture, aortic dissection
Embolic	From aortic vessels, mitral valvulopathy
Atherosclerothic	Of aortic branches
Compressive	Spinal disc herniation
Arteritis	Syphilis, vasculitis
Anemia	Sickle cell disease
Iatrogenic	Arteriography, aortic surgery
Traumatic	Vertebral occlusion by neck trauma

There have been relatively few studies on long-term outcome after spinal cord infarctions. However, many patients experience significant improvement and from 35 to 71 % of the patients unable to walk in the acute phase regain the ability to walk on long-term follow-up, depending on lesion site and size.

Thus, patients with spinal cord infarction were more likely to be discharged home probably for the lack of cognitive deficits. Mortality rate is about 9 % and is associated with age, severity of deficits in the acute phase, and peripheral vascular disease

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Vascular Diseases: Cerebral Hemorrhage

2

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Key Facts

- **Definitions** – Intracerebral hemorrhage (ICH) refers to bleeding within the brain parenchyma.
- **Demographics** – ICH is the second most common form of stroke accounting for 10–30 % of first-ever strokes.
- **Clinical features** – Acute neurological deficits often accompanied by vomiting, seizures, headache, increased diastolic blood pressure, neck stiffness, coma.
- **Diagnostic markers**
  - **Risk factors** – Older age, hypertension, alcohol intake, cerebral amyloid angiopathy.
  - **Genetics** – Apolipoprotein E gene and its ε2 and ε4 alleles are associated with ICH in CAA. Hereditary cerebral amyloid angiopathy caused by mutations in the APP, CST3, ITM2B, or transthyretin gene is inherited in an autosomal dominant pattern.
  - **Imaging** – CT: acute blood is markedly hyperdense compared to brain parenchyma. MRI: appearance of blood changes depends on the sequence, the time since the hemorrhage, the size and location of the bleeding. CT-MRI-angiography: to assess for underlying vascular anomaly.
- **Therapy** – Supportive treatment and correction of related risk factors.
- **Prognosis** – The 30-day mortality is up to 35–50 %. Half the deaths occur in the acute phase, mostly in the first 48 h. Full functional recovery at 6 months is expected in 20 % of survivors.

Abbreviations

ACA, anterior cerebral artery; AHA/ASA, American Heart Association/American Stroke Association; AOH, acute obstructive hydrocephalus; APP, amyloid precursor protein; AVM, arteriovenous malformations; BP, blood pressure; CAA, cerebral amyloid angiopathy; CMs, cavernous malformations; CCM, cerebral cavernous malformations; CST3, cystatin C; CTA, CT angiography; DAVFs, intracranial dural arteriovenous fistulas; DVA, developmental venous anomaly; DVT, deep vein thrombosis; EUSI, European Stroke Initiative; FUNC, functional outcome risk stratification; HE, hematoma expansion; ICH, intracerebral hemorrhage; IA, intracranial (cerebral) aneurysm; ICP, intracranial pressure; ITM2B, integral membrane protein 2B; IVH, intraventricular hemorrhage; MCA, middle cerebral artery; MMD, Moyamoya disease; PCA, posterior cerebral artery; PCH, primary cerebellar hemorrhage; PHE, perihematomal edema; SAH, subarachnoid hemorrhage; SRS, stereotactic radiosurgery; VTE, venous thromboembolic event

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2.1 Spontaneous Intracerebral Hemorrhage

2.1.1 Definitions and Epidemiology

Intracerebral hemorrhage (ICH) refers to bleeding within the brain parenchyma.

ICH is the second most common form of stroke accounting for 10–30 % of first-ever strokes and is a major cause of morbidity and mortality worldwide [1].

2.1.2 Clinical Features and Risk Factors

It is difficult to distinguish the ICH clinical presentation from ischemic stroke. Those subjects presenting with acute neurological deficits accompanied by vomiting, seizures, headache, increased diastolic blood pressure, neck stiffness, and coma have a higher likelihood of ICH occurrence compared to those with ischemic stroke. However, only neuroimaging can support the definitive diagnosis.

Main risk factors for ICH include male gender, older age, hypertension, alcohol intake, cerebral amyloid angiopathy (CAA), and Asian origin [2–4].

Diabetes mellitus and current smoking are considered weak risk factors [4].

Hypertension-related ICH is typically observed in deep brain structures and its risk increases with increasing blood pressure values [4, 5].

Alcohol intake–related ICH risk appears to be dose dependent, with higher risk among those subjects with higher daily alcohol intake.

Data regarding lipid levels are controversial. Low serum triglyceride levels (≤0.4 mmol/L) were associated with an increased risk of ICH [6].

Oral anticoagulants and sympathomimetic drug abuse [7] also increase the likelihood of ICH. In subjects under warfarin, the ICH risk is 0.3–1 % per patient-year, while a significant increase of ICH risk is detected when the international normalized ratio is >3.5 [8].

CAA more likely occurs in older ages, and CAA-related ICH appears to be observed mostly in lobar regions. Apolipoprotein E gene and its ε2 and ε4 alleles are associated with ICH in CAA [9]. Hereditary cerebral amyloid angiopathy caused by mutations in the APP (amyloid precursor protein), CST3 (cystatin C), ITM2B (integral membrane protein 2B), or transthyretin gene is inherited in an autosomal dominant pattern.

2.1.3 Diagnostic Markers

Brain CT and MRI are the most widely employed tools for an early diagnosis. Neuroimaging provides some crucial prognostic information, such as the hematoma location, volume, and extension either within the intracerebral parenchyma or into the ventricular system, and the presence of surrounding edema with a possible consequent mass effect with midline shift (Fig. 2.1).

CT is the most used technique in ICH diagnosis since it is generally more readily available and rapidly carried out.

MRI is equivalent to CT for the evaluation of acute ICH. The gradient-echo imaging technique with T2 weighting is the best option to detect ICH in the acute phase. Furthermore, MR angiography might provide both secondary causes of ICH and information about the intracranial vasculature (arterial and venous).

Since up to 15 % of subjects with ICH carry vascular abnormalities as a potential cause of ICH, CT angiography (CTA) is more often utilized in acute settings in order to clarify the etiology of ICH. CTA may detect the so-called spot sign (i.e., contrast extravasation [>1–1.5 mm]), which could be interpreted as a marker of ongoing bleeding, risk for hematoma expansion, and poor outcome.

2.1.4 Therapy

Acute Management

Airway: prompt intubation is the preferred approach in non-conscious patients.

Blood pressure: guidelines recommending blood pressure treatment are available by the

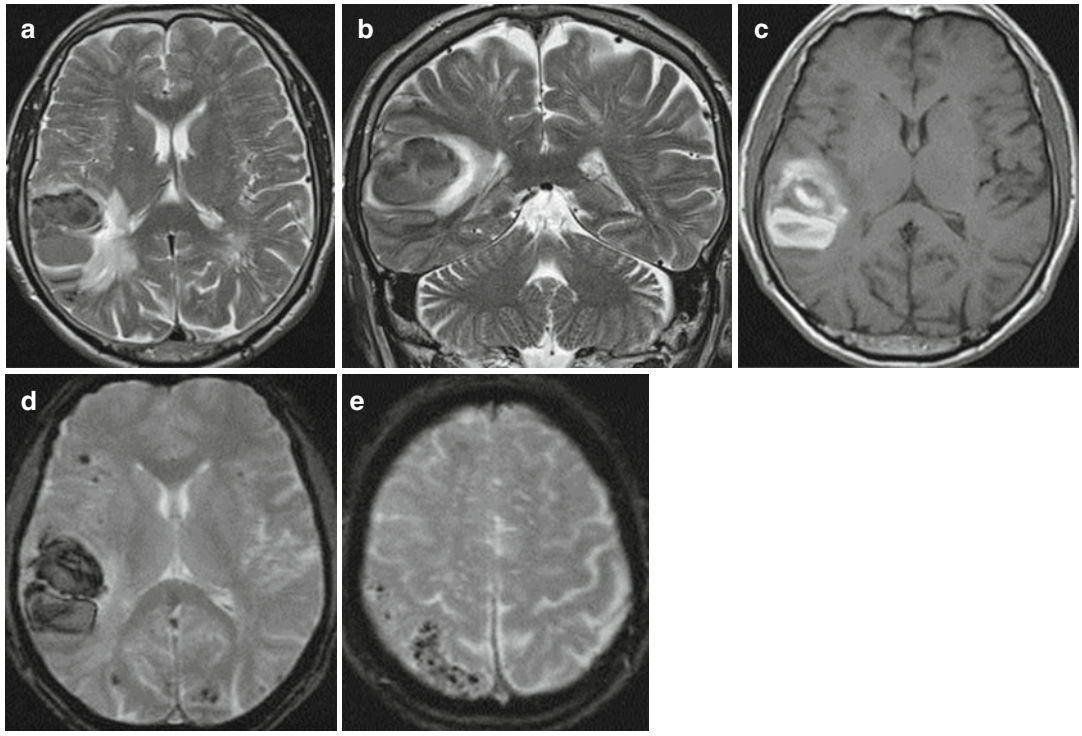

Fig. 2.1 Intracranial hemorrhage in cerebral amyloid angiopathy. Axial and coronal T2- and axial T1-weighted images (**a**–**c**) demonstrate a large right intracranial hemorrhage with perilesional edema. Axial T2*-weighted gradient-echo images, (**d**, **e**), reveal multiple and bilateral microhemorrhages mostly located in the cortex

American heart Association/American Stroke Association (AHA/ASA) [10] and the European Stroke Initiative (EUSI) [11].

Hemostatic therapy: ongoing bleeding might be prevented by an early correction of an underlying coagulopathy.

Intracranial pressure (ICP): ICP monitoring and treatment are advised if Glasgow Coma scale score ≤8, transtentorial herniation, significant IVH, or hydrocephalus.

Hyperglycemia: a careful glycemic control in the early phase is mandatory [10].

Temperature: fever control would lower mortality and improve outcome.

Seizures: antiepileptic drugs should not be used routinely (AHA/ASA recommendation). Indications are, indeed, the presence of clinical or electroencephalographic seizures in patients with a deterioration of mental status [10].

2.1.5 Prognosis

ICH carries the worst prognosis of all acute cerebrovascular diseases [1]. Half the deaths occur in the acute phase, mostly in the first 48 h [1, 12]. The 30-day mortality for ICH has been reported up to 35 % and 50 % in "developed and developing countries," respectively [2]. Full functional recovery at 6 months is expected in only 20 % of survivors [1]. An early and effective treatment is crucial in order to avoid the occurrence of ICH complications, which are the major predictors of early mortality and poor outcome.

ICH complications include hematoma expansion (HE), perihematomal edema (PHE), intraventricular hemorrhage (IVH) with hydrocephalus, venous thromboembolic events, seizures, hyperglycemia, hypertension, infections, and fever [13] (Table 2.1).

Table 2.1 ICH complications

	Definition and characteristics	Risk factors	Outcome
Hematoma expansion (HE)	Increase in volume (33–50 %) Absolute change in hematoma volume (1.5–20 mL) on repeat CT scan	"Spot sign" Large hematoma volume at presentation Early presentation (≤3 h) Heterogeneity of hematoma density on CT scan Warfarin use	Every 10 % increase in ICH growth (by CT scans within 24 h): 5 % increased risk of death 16 % increased risk of worsening outcome 18 % increased risk of poor outcome evaluated on the Barthel index or poor functional independency
Perihematomal edema (PHE)	Increase in volume by 75 % in the first 24 h Strong increase during the first week and maximum during the second week after bleeding	Hyperglycemia Disorder of the coagulation factors Statins Increase of systolic blood pressure	Unclear correlation with clinical outcome and mortality
Intraventricular hemorrhage (IVH)	Common after ICH (30–50 % of patients)	Mean arterial pressure >120 mmHg at baseline Large ICH at baseline	Poor functional outcome and high overall mortality (50–75 %), mostly at presentation 30-day mortality rate: 43 % in ICH with IVH vs. 9 % in ICH without IVH IVH growth increases risk of death or severe disability at 90 days Patients with ICH + IVH total volume >40 mL have ~40 times more probability to have a poor prognosis Patients with ICH + IVH total volume >50 mL have 100 % unfavorable outcome
IVH and hydrocephalus	Extension of ICH into the ventricles with direct mass effect of ventricular blood, up to acute obstructive hydrocephalus (AOH) 50 % of IVH due to ICH develop AOH by obstruction of the third and fourth ventricle	*AOH more commonly related to:* Large IVH Thalamic hemorrhages	AOH in IVH reduces the chance of positive outcome (from 15.1 to 11.5 %)
Seizures	50–70 % occur within the first 24 h 90 % in the first 3 days Overall 30 day risk: 8 % Early seizures: occurred <2 weeks Late seizures: occurred >2 weeks	Increased midline shift on 48–72 h follow-up CT scan is independently associated with seizures	Early seizures are *predictive* of epilepsy
Venous thromboembolic events (VTE)	Rate of symptomatic VTE: 3–7 % Risk of pulmonary embolism 1–2 %; deep vein thrombosis (DVT) 1–4 % Subclinical DVT up to 17 %	Severe stroke Advanced age Lengthy immobilization Increased prothrombotic activity	Worse incidence of DVT in black patients Women at greater risk of VTE VTE is associated with a 30-day mortality rate of 35–52 %

Table 2.1 (continued)

	Definition and characteristics	Risk factors	Outcome
Fever	Direct consequence of accompanying infections or brain damage Observed in up to 40 % of ICH patients	Early rise in body temperature is a great risk factor for adverse outcome	Poor outcome (relative risk increased by 2.2 times) worsened by a longer duration of fever Increased mortality (by a factor of 1.8 for each 1 °C increase in baseline body temperature)
Hyperglycemia	A response to stress and severity of ICH About 60 % of ICH patients may develop hyperglycemia	Hyperglycemia associated with larger hematoma size	Predictor of early mortality and worse functional outcome in non-diabetic patients with ICH Predictor of 30-day mortality in diabetic and non-diabetic patients with ICH
Increased blood pressure (BP)	BP ≥140/90 mmHg occurred in >70 % of ICH patients Unknown mechanism for BP increase, most likely a multifactorial process	Associated with HE, PHE, rebleeding	Worse outcome Increased mortality, but similar poor outcome for systolic BP <120 and >220 mmHg

Table 2.2 ICH score (*The higher the score, the greater the mortality)*

Parameter	Points
Glasgow Coma scale 3–4, 5–12, 13–15	2, 1, 0
Hematoma volume (≥30 cm^3)	1
Intraventricular hemorrhage	1
Infratentorial localization	1
Age ≥80 years old	1
Thirty-day mortality (points; % of mortality)	**1 (13 %), 2 (26 %), 3 (72 %), 4 (97 %), 5 (100 %)**

From: Hemphill et al. [14]

Adverse outcome with increased early mortality during the hyperacute phase is often related to HE, IVH with hydrocephalus, and hyperglycemia [13].

Poor outcome with early neurological deterioration is similarly associated with HE, hydrocephalus, and PHE.

"ICH score" [14] is a simple, reliable grading scale developed to predict the *30-day mortality*, using features as the Glasgow Coma scale, intracerebral hematoma volume, IVH, infratentorial location, and age. The higher the score, the greater the mortality (Table 2.2).

Moreover, the ICH score is a useful grading scale for *long-term functional outcome* after acute ICH. The score stratifies subjects with regard to 12-month functional outcome as assessed by modified Rankin scale [15].

Additionally, a suitable score (i.e., the "functional outcome risk stratification [FUNC] score") is assessed in order to perform a prediction model for ICH functional outcome [16]. Rather than mortality, the FUNC score predicts the *functional independence at 90 days* by using similar features of ICH score (Table 2.3). The higher the FUNC score, the greater the possibility for a functional independence.

2.2 Primary Cerebellar Hemorrhage

Primary cerebellar hemorrhages (PCHs) are spontaneous hemorrhages in the cerebellar parenchyma, caused neither by tumor, vascular malformation, or aneurysm nor by a trauma. PCHs are roughly 10 % of all ICH and about 15 % of cerebellar strokes. The clinical features regard the anatomy of the posterior fossa. Conditions related to the

Table 2.3 FUNC score [16] (*The higher the score, the greater the possibility for a functional independence)*

Component	Points
ICH volume (cm^3)	
<30	4
30–60	2
60	0
Age (years)	
<70	2
70–79	1
≥80	0
ICH location	
Lobar	2
Deep	1
Infratentorial	0
Glasgow Coma scale score	
≥9	2
≤8	0
Total FUNC score (points; % of patients with functional independence at 90 days)	**0–4 (0 %), 5–7 (13 %), 8 (42 %), 9–10 (66 %), 11 (82 %)**

blockage of the fourth ventricle thus creating an obstructive hydrocephalus and/or compression of the brainstem might determine a decision of a rapid life-saving surgical treatment.

The most relevant complications are brainstem compression, hydrocephalus, and brain herniation.

A recent comprehensive review evaluated all studies and case reports with PCH from 1927 to 2011 [17]. Since many data were not actually comparable because of group heterogeneity, the authors provided only studies of mortality with data on treatment regimens. The overall mortality rate was 30.9 %, distinguishing 33.3 % for the medical, and 29.1 % for the surgical group. However, the clinical outcome in survivors of PCH was slightly in favor of a conservative treatment. This might be related to the fact that the patients who underwent surgery were treated for life-threatening complications, and were, therefore, already at a higher risk of death compared to those treated conservatively.

2.3 Intracranial Hemorrhage Due To Vascular Malformations

Key Facts

- **Terminology and definitions** – Intracranial hemorrhage due to arteriovenous malformations (AVM), aneurisms, cavernous malformation (CM), intracranial dural arteriovenous fistulas (DAVFs), Moyamoya disease (MMD).
- **Epidemiology** – Prevalence 15–18/100,000 adults (AVM); 9–20/100,000 persons/year (SAH); 0.4–0.6 % (CMs); 10–15 % of all intracranial vascular abnormalities (DAVFs); 0.35–0.54 per 100,000 (MMD).
- **Clinical features** – Acute or chronic focal neurological deficit due to intraparenchymal hematoma or mass effect (AVM, CM, DAVFs, MMD) or to ischemic-hemorrhagic lesion (MMD); sudden onset of a severe headache (i.e., "thunderclap headache: the worst headache of my life," neck pain, and rigor) (SAH).
- **Diagnostic markers**
  - **CSF** – Red blood cells (SAH).
  - **Genetics** – Hereditary CMs: 50 % of patients with onset of bleeding before 15 years carry CCM3 mutations. Early bleeding occurs in 26 % and 39 % of patients with CCM1 and CCM2 mutations, respectively.
- **Imaging** – Acute bleeding: urgent CT scan; lumbar puncture (in SAH when unclear CT), and/or CT angiography of the brain; MRI – MR angiography; digital subtraction angiography.
- **Prognosis**
  - **Principles of treatment** – Surgery (CMs, MMD), stereotactic radiosurgery, embolization (AVM, SAH); surgery (DAVFs).
  - **Disability** – Permanent neurological deficits or death: median 7.4 % after microsurgery; 5.1 % after stereotactic radiosurgery; 6.6 % after embolization (AVM). Survival 65 % (SAH); about one-third of subjects remain *dependent* in *activities* of *daily* living (SAH); permanent morbidity in 27 % (CMs). Successful interventional treatment 75 % of patients, 1/3 of patients with residual symptoms (DAVFs). Overall stroke risk: 3.2 %/year for asymptomatic MMD. For symptomatic MMD the 5-year risk of recurrent ipsilateral stroke is 65 % if medically treated, and 17 % in the group admitted to surgery.

2.4 Cerebral Arteriovenous Malformations (AVMs)

2.4.1 Definitions and Epidemiology

AVMs are abnormal connections between arteries and veins, thus leading to arteriovenous shunting with the presence of the so-called nidus (network of vessels). The prevalence of AVM is 15–18 per 100,000 adults [18]. The overall detection of incidental AVM is 1 per 100,000 adults/year [19].

Risk of Hemorrhage The first-ever hemorrhage rate is 0.55/100,000 person-years [19]. The hemorrhagic risk is higher (4.5–34 %) in previously ruptured brain AVMs (with deep venous storage and deeply seated); the risk is lower in unruptured AVMs (0.9–8 %) [20].

The risk of subsequent hemorrhage is higher in case of the following: (1) deep venous drainage, (2) brain AVM presentation with hemorrhage, (3) association with aneurysms, (4) deep location [20, 21].

2.4.2 Prognosis

Intracranial hemorrhage rates are 1.4 per 100 person-years *overall*; 0.18 per 100 person-years *after microsurgery*; 1.7 per 100 person-years *after stereotactic radiosurgery (SRS)*; 1.7 per 100 person-years *after embolization* [22]

Lower hemorrhage rates and lower case fatality in the following: (1) male sex, (2) small brain AVMs, (3) younger age, (4) brain AVMs with Spetzler-Martin grade I–III, (5) lower proportions of eloquent brain AVMs and higher proportions of obliterated brain AVMs [22].

After Treatment Low case fatality in patients treated with SRS; high hemorrhage rates during follow-up after SRS and embolization, and low after microsurgery [22].

Complications After Treatment Permanent neurological deficits or death in a median 7.4 % (range, 0–40 %) of patients after microsurgery; 5.1 % (range, 0–21 %) after SRS; 6.6 % (range, 0–28 %) after embolization [22].

Successful Brain AVM Obliteration In 96 % (range, 0–100 %) of patients after microsurgery; 38 % (range, 0–75 %) after SRS; 13 % (range, 0–94 %) after embolization [22].

The ARUBA trial showed that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke in patients with unruptured brain arteriovenous malformations followed up for 33 months [23].

2.5 Subarachnoid Hemorrhage (SAH) Due To Intracranial Aneurysms

2.5.1 Terminology and Definitions

Intracranial aneurysms are a localized dilation or ballooning of intracranial blood vessels.

2.5.2 Epidemiology

The rupture of intracranial aneurysms represents up to 85 % of nontraumatic SAH [24]; the overall incidence of SAH is 9–20 per 100,000 person-year. The prevalence of unruptured intracranial aneurysms is 3.2 % [25]. SAH is more frequent in women; the mean age of presentation is 55 years.

Major risk factors of hemorrhage are current or former history of smoking, alcohol intake, and hypertension.

Minor risk factors of hemorrhage are cocaine addiction (with younger patients having the worse outcome), genetic conditions (first-degree family history, Marfan and Ehler-Danlos syndrome, polycystic kidney disease).

Higher risk factors of aneurysm rupture are previous SAH, age >60 years, female gender, Finnish or Japanese origin, size of aneurism >10 mm, and localization in the posterior circulation.

Classical presentation is characterized by sudden onset of severe headache, ("thunderclap headache"), with rigor accompanied by vomiting from increased intracranial pressure. Less severe hemorrhages may cause nonspecific symptoms. Indicators of meningeal irritation occur in 80 % of patients. Photophobia is common. Focal neurological deficits may also occur.

2.5.3 Prognosis

A 7.2 % of subjects die within 60 days [26]. One-third of those subjects who survive the first month remain dependent with respect to daily activities during their whole life. Quality of life remains reduced even with recovered independence [26].

Poor outcome at 3 months in case of the following: (1) older age, (2) worse admission grade (at Glasgow Coma scale, and Motor deficit of the World Federation of Neurological Surgeons grading scale), (3) concomitant cerebral infarction, (4) symptomatic vasospasm, (5) posterior circulation aneurysms, (6) intraventricular and intracerebral extension of the hematoma, (7) high systolic blood pressure at admission, and (8) great clot thickness on CT scan at admission [26, 27].

Vasospasm Angiographic vasospasm is detectable in up to 70 % of cases, and occurs with neurological deficit in 30 % of cases. Delayed cerebral ischemia (due to vasospasm) can occur days after the index SAH and possibly is a deadly complication.

2.6 Cavernous Malformations (CMs)

2.6.1 Terminology and Definitions

CMs consist of endothelium-lined dilated spaces with deficiency in both the smooth muscle layer and the tight junction and with occurrence of thrombosis and calcification.

2.6.2 Epidemiology

Prevalence of CMs are 0.4–0.6 % [28]. Sporadic or hereditary CMs account for 5–10 % of all cerebral vascular malformations, and roughly 20 % of them are located in the brainstem [29]. Most CMs remain clinically quiescent. CMs located in neurologically eloquent areas are prone to become symptomatic, often with seizure.

CMs can cause extra-lesional hemorrhage (beyond the confines of the cavernoma) or intra-lesional hemorrhage (within the cavernoma itself).

2.6.3 Medical therapy

In patients managed conservatively hemorrhage rates varies between 0.25 and 4.5 % per person/year [30]. The overall risk of first hemorrhage in patients with sporadic lesions ranges between 0.4 and 0.6 % per person/year. The overall risk of first hemorrhage in familial cases is 1.4 % per person/year. The risk of recurrent hemorrhage after a first intracerebral hemorrhage varies from 3.8 to 33.9 % per year [31].

Brainstem CMs annual rehemorrhage rate is 5.1 % for untreated patients [32]. The adverse factors for preoperative rehemorrhage risk regard age (≥50 years), perilesional edema, and size ≥20 mm [29]. Risk factors for postoperative hemorrhage are the presence of a developmental venous anomaly and an incomplete resection. The postoperative annual hemorrhage rate was 0.4 % [29].

2.6.4 Prognosis

Brainstem CMs with developmental venous anomalies have, therefore, more frequent hemorrhages than those without [32].

Brainstem CMs [29]: 35.1 % worsen immediately after surgery with total recovery in up to ~60 % within 6 months; at a mean follow-up of 89.4 months ~60 % improve, ~30 % remain unchanged, and ~10 % worsen.

Permanent morbidity affects 26.9 % of patients.

Increased age, multiple hemorrhages, ventral-seated lesions, and poor preoperative status are adverse factors for a favorable long-term outcome.

Hereditary CMs De novo lesions are 0.2–0.4 per year; their bleeding rate is 1.1–4.3 % per lesion-year [33].

Fifty percent of patients with onset of bleeding before 15 years carry CCM3 mutations (causing 10–15 % of hereditary cerebral cavernous malformations). Early bleeding can also occur in 26 % and 39 % of patients with CCM1 and CCM2 mutations, respectively.

Treatment Resection of superficial hemispheric lesions is usually successful and uneventful. The management of hemorrhagic cavernous malformations must be individualized.

2.7 Intracranial Dural Arteriovenous Fistulas (DAVFs)

2.7.1 Terminology and Definitions

DAVFs refer to pathological shunts between dural arteries and dural venous sinuses, meningeal or cortical veins.

The presence of a dural arterial supply and the absence of a parenchymal nidus distinguish DAVFs from pial or parenchymal AVM.

2.7.2 Epidemiology

The prevalence of intracranial DAVFs is 10–15 % of all intracranial vascular abnormalities [34]. Risk of hemorrhage is increased by male gender, cortical venous drainage with venous varices, and tentorial DAVFs [35].

2.7.3 Prognosis

The majority of DAVFs is completely obliterated (75 %) by specific treatments: endovascular, surgical and, to a lesser extent, gamma-knife surgery [35]. Individualized treatment achieves excellent outcomes.

About two-thirds of patients with the hemorrhagic presentation have a full recovery with no or marginal residual symptoms [35].

2.8 Moyamoya Disease (MMD)

2.8.1 Terminology and Definitions

Moyamoya disease (MMD) is a chronic occlusive cerebrovascular disease involving progressive stenosis of the terminal portion of the internal carotid arteries and/or the proximal portions of the anterior cerebral arteries and middle cerebral arteries.

MMD has two main neuropathological patterns defined as ischemic and hemorrhagic. In the Japanese literature, opposed to that observed in the USA, the ischemic type predominates in childhood, while the hemorrhagic type is more often observed in the adult population.

MMD may be asymptomatic (i.e., Moyamoya phenomenon without clinical events and without radiological infarction).

The natural course of MMD is poorly understood, but revascularization surgery is believed to be an effective procedure for preventing the progression of clinical symptoms.

The natural history of hemorrhagic Moyamoya disease is poor because of a high rate of recurrent bleeding attacks.

2.8.2 Epidemiology

The prevalence in Japan is estimated to be 0.35–0.54 per 100,000 [36]. The prevalence in the European population is one tenth of the incidence in the Japanese population. In the USA, most of the adults present with ischemic symptoms, and 14.6 % has a hemorrhagic onset [37], uncommon in children.

Risk of hemorrhage in adults is more often associated with intracranial aneurysms, ACA occlusion, fetal-type PCA, and MCA occlusion with collateral flow, whereas ACA occlusion was

mostly associated with deep intracerebral hemorrhage or IVH [38].

Independent risk factors for hemorrhage are associated to anterior choroidal artery and posterior communicating artery dilation [39]; cerebral microbleeds mostly close to the midline structure or in deep brain areas.

2.8.3 Prognosis

The annual risk for stroke (hemorrhagic or ischemic) is 3.2 % per year in asymptomatic Moyamoya patients [40]. In symptomatic, medically treated Moyamoya patients, the 5-year risk of recurrent ipsilateral stroke is 65%, while it is 17 % in the group admitted to surgery, including the perioperative and subsequent ipsilateral stroke risk [41]. In the Japanese population, during a 5-year follow-up in hemorrhagic Moyamoya, rebleeding attacks occurred in 11.9 % and 31.6 % of patients surgically or conservatively treated, respectively [42].

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Inflammatory Diseases of Cerebral Arteries

3

Marco Longoni and Elio Agostoni

Abbreviations

APS, antiphospholipid antibody syndrome; BD, Behçet disease; CNS, central nervous system; CSF, cerebrospinal fluid; EDSS, modified expanded disability status scale; GCA, giant cell/Hoton arteritis; HR, hazard ratio; MRI, magnetic resonance imaging; (m-)RS, (modified-) Rankin score; MS, multiple sclerosis; NBD, neuro-Behçet disease; NP-SLE, neuropsychiatric SLE; NS, Neurosarcoidosis; OR odds ratio; PACNS, primary angiitis of central nervous system; PNS, peripheral nervous system; PSS, primary Sjögren syndrome; RCVS, reversible cerebral vasoconstriction syndrome; m-RS, modified-Rankin Score; SA, sarcoidosis; SLE, systemic lupus erythematosus

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3.1 Primary Angiitis of Central Nervous System (PACNS)

Key Facts

- **Terminology and definitions** – Vasculitides of brain arteries are isolated inflammation and necrosis of cerebral vessels without other systemic involvement.
- **Clinical features** – Most commonly headache. Cognitive impairment can be insidious. Stroke and transient ischemic attacks. Seizures. Cranial nerve involvement, including ocular nerves.
- **Diagnostic markers**
  - **Biopsy** – Gold standard. Angiography and clinical history.
  - **CSF** – May show aseptic meningitis.
  - **MRI** – Ischemic and hemorrhagic lesions. AngioMR or conventional angiography shows patchy narrowing or dilatation of cerebral arteries.
- **Top differential diagnoses** – Reversible cerebral vasoconstriction syndrome (RCVS), multiple sclerosis, systemic diseases and infections, neoplasms, CADASIL.
- **Principles of treatment** – Steroids and immunosuppressive drugs may be efficacious.
- **Prognosis** – Higher mortality than in control population. Frequent relapses. Persistent disability.

3.1.1 Definition

Primary angiitides (vasculitides) of central nervous system (PACNS) are isolated inflammation and necrosis of cerebral vessels without systemic involvement.

3.1.2 Demographics

Primary angiitis of the CNS is a rare disorder. Until 2007, no more than 500 cases had been described in the international literature. The peak of incidence is at 50 years with no clear sex preponderance.

3.1.3 Clinical Features

The clinical signs and symptoms are nonspecific and reflect the diffuse or patchy nature of the pathological process. The course of the illness is also variable with presentations ranging from hyperacute to chronic and insidious. Headache is the most common symptom and may vary in quality, intensity, and pattern. Thunderclap headache is almost never reported in PACNS and should indicate a diagnosis of reversible cerebral vasoconstriction syndrome (RCVS). Cognitive impairment is also common and can be insidious. Stroke and transient ischemic attacks occur in 30–50 % of patients with PACNS. Stroke usually affects many different vessels; presentation of PACNS as a single stroke is uncommon. Cranial nerve involvement includes ocular nerves, myelopathy seizure and ataxia might also be present.

Two different forms of PACNS are described:

- PACNS with positive brain biopsy (after negative angiography), in which headache and cognitive impairment are more common and can be associated to seizures and CSF alterations (pleocytosis and high protein levels).
- PACNS with positive angiography and usually focal neurological deficits [1].

Other rare subsets of primary CNS vasculitis are: (a) form with prominent leptomeningeal enhancement on MRI, (b) primary CNS vasculitis presenting with a solitary tumor-like mass lesion (4 % of cases), (c) angiitis associated with cerebral amyloid angiopathy [2].

3.1.4 Diagnostic Markers

The most widely accepted diagnostic criteria include [3]: (1) clinical and instrumental/histological criteria, (2) angiographic or histopathological findings of CNS angiitis, (3) no evidence of systemic vasculitis or of conditions to which the angiographic or pathologic findings could be secondary.

3.1.5 Laboratory

CSF CSF analysis is performed to rule out infectious or malignant diseases. Aseptic meningitis with modest lymphocytic pleocytosis (usually <20 range 0–575 cells/mL), and a median CSF protein concentrations (<120 mg/dL), might be found. Oligoclonal bands and increased IgG synthesis are rare.

3.1.6 Imaging

Conventional angiography showing alternating areas of stenosis and dilatation (sensitivity of 40–90 %, and specificity of 30 %) is the gold standard imaging investigation for the diagnosis [4, 7, 8].

MRI abnormalities in PACNS include alterations of subcortical white matter, deep gray and white matter, and cerebral cortex. Multiple infarcts often occur [4]. Pseudo-tumoral lesions are present in 4 % of PACNS [5]. Gadolinium enhancement of the leptomeninges takes place in 8 % of patients, and may constitute a target for biopsy. Arterial wall enhancement on high resolutions MRI is a further diagnostic tool [6].

Brain Biopsy Cerebral and meningeal biopsy is the gold standard for the diagnosis of primary CNS vasculitis. Primary CNS vasculitis (histopathologically: granulomatous, lymphocytic, and necrotizing) most often affects small and medium-sized leptomeningeal and parenchymal arterial vessels [9].

3.1.7 Therapy

In the absence of randomized clinical trials, high-dose glucocorticoids (prednisone 1 mg/kg per day) or intravenous pulse methylprednisolone seems to be the best treatment to achieve disease control in PACNS.

Immunosuppressive therapy is often started after steroids; cyclophosphamide for 3–6 months being the first choice. Alternative immunosuppressants (azathioprine, mycophenolate, methotrexate) can be used.

Patients with primary CNS vasculitis and cerebral amyloid angiopathy might also respond to glucocorticoids alone, but often cyclophosphamide has to be added to obtain a satisfactory response. In patients with primary CNS vasculitis presenting as a tumor-like mass lesion, aggressive immunosuppressive therapy is associated with better outcomes than glucocorticoids alone.

3.1.8 Prognosis

In primary CNS vasculitis, survival is reduced by 30–35 % at 7 years after diagnosis (Fig. 3.1) [8].

Patients with several bilaterally affected large vessels, who rapidly progress with the disease and who suffer numerous recurrent cerebral infarction are more prone to a fatal outcome. By contrast, patients with small vessel vasculitides, prominent leptomeningeal enhancement, negative cerebral angiogram, and positive brain biopsy typically respond rapidly to treatment and have a positive neurological prognosis (Fig. 3.1).

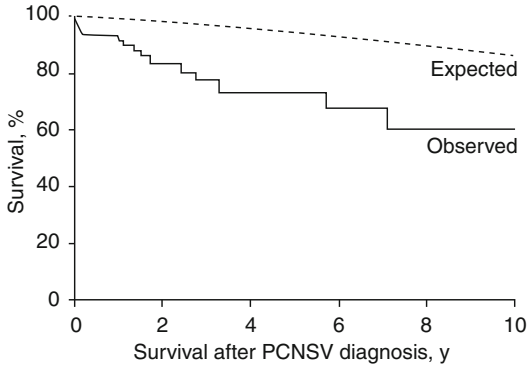

Fig. 3.1 Age- and sex-adjusted survival of patients with primary central nervous system vasculitis (*PCNSV*) versus estimated survival of the US white population ($p < 0.001$)

A lower mortality rate has also been observed in patients with MRI gadolinium enhancement of cerebral lesions or the meninges [11]. Some reports have suggested that patients with primary CNS vasculitis diagnosed on the basis of abnormal angiography alone have a more benign course than do those diagnosed by biopsy (particularly in pediatric patients) [12, 13]. However, in other series, the clinical characteristics and outcomes in patients diagnosed by biopsy and angiography were similar [8, 14, 15]. The inclusion of patients who are clinically suggestive of reversible cerebral vasoconstriction syndrome, which usually has a benign course, might account for these differences.

In a case series of 101 patients, mortality was higher than expected [8]. Four indicators at presentation were associated with an increased mortality rate: (1) focal neurological deficit versus headache or constitutional symptoms (HR, 3.60), (2) cognitive impairment versus headache or constitutional symptoms (HR, 4.00), (3) cerebral infarction versus no infarction (HR, 4.39), and (4) large vessel involvement versus small vessel involvement (HR, 7.93) [8].

In addition, disability defined by modified-Rankin Score (m-RS) was directly linked to these factors. Indeed, high disability scores (Rankin scores, 4–6) at last follow-up were associated with presenting manifestations of focal neurological deficit or stroke (OR, 4.09), cognitive impairment (OR, 7.36), cerebral infarction at diagnosis (assessed by MRI; OR, 4.46), and large-vessel involvement (OR, 3.23) [8].

No differences in survival were observed in patients stratified according to treatment (prednisone alone vs prednisone and cyclophosphamide), diagnostic technique (angiography vs biopsy), or other biological or laboratory markers.

The overall mortality rate of the cohort with PCNSV increased, but most survivors improved with relatively low disability scores. Patients with Rankin score of 0–2 at diagnosis continued to have low scores (0–3) at last follow-up evaluation, and most of the patients with severe disability at diagnosis (Rankin score, 4–5) had a disability at follow-up [8].

Fifty-two adult PACNS patients (51 treated with steroids, 44 patients received cyclophosphamide) with a median follow-up of 35 months had a mortality rate of 6 % [15]. Response to first-line steroid therapy was significant in 65 % of cases, 8 % did not respond, and relapses occurred in 27 % [15].

Neurologic damage persisted for 40 survivors (82 %). At last follow-up visit, the modified-Rankin scale score had declined to a median score of one (range 0–5), and 79 % of survivors had scores of two [15]. Finally, in the same cohort, the presence of seizures and the presence of gadolinium-enhanced lesions were predictive of clinical relapses [15].

3.2 Vasculitis Complicating Systemic Diseases

3.2.1 Behçet Disease

Key Facts

- **Terminology and definitions** – Behçet: is a multisystem relapsing inflammatory disorder.
- **Clinical features** – Neurological lesions in Behcet disease may be: (1) parenchymal (subacute brainstem syndromes; cranial nerve, cerebellar, corticospinal involvement) and (2) non-parenchymal mostly characterized by sinus venous thrombosis.
- **Diagnostic markers** – Focal CNS deficits with mouth and genital sores, uveitis, arthropathies, skin rashes, and dermographism characterize parenchymal Neuro-Behçet; headache and a pseudotumor cerebri–like picture indicate non-parenchymal neuro-BD.
- **Laboratory** – CSF may show aseptic meningitis.
- **Imaging** – Diffuse lesions in the brainstem or basal ganglia extending to the diencephalon are the most common parenchymal findings.
- **Top differential diagnoses** – Multiple sclerosis, SLE, sarcoidosis.
- **Prognosis** – Mortality rate may be high. In parenchymal forms disability is frequent, whereas non-parenchymal NB has a better prognosis.
- **Principles of treatment** – Steroids and immunosuppressive therapy might be efficacious in parenchymal form. Anticoagulation plays a pivotal role in cases of venous thrombosis.

3.2.1.1 Terminology and Definitions

Behçet disease (BD) is a multisystem relapsing inflammatory disorder of unknown cause characterized by recurrent orogenital ulcers, ocular inflammatory disease, thrombophlebitis, and various cutaneous manifestations.

3.2.1.2 Demographics and Clinical Features

Neuro-Behçet disease (NBD) occurs in 10–49 % of patients with BD; male predominance is 4:1 [16, 17].

Two different clinical syndromes are described. The most common form, due to an immune-mediated meningoencephalitis, involves the brainstem and is called parenchymal Neuro-Behçet. The second one, named non-parenchymal NBD, is the consequence of thrombosis and inflammation within the dural venous sinuses and, rarely, within the cerebral arteries [17, 18]. Parenchymal CNS involvement is often a subacute brainstem syndrome with cranial nerve findings, dysarthria, and cerebellar or corticospinal tract signs. Uncommon presentations include stroke-like episodes, seizures, and psychiatric features.

Non-parenchymal NBD is mostly characterized by sinus venous thrombosis that may result in intracranial hypertension with headache, vomiting, and bilateral papilledema. Arterial involvement is rarer and leads to ischemic stroke or subarachnoid hemorrhage.

Neurological symptoms represent the first manifestation of Bechet only in 3 % of cases [18].

3.2.1.3 Diagnostic Markers

The diagnosis of Behcet's disease is entirely based on clinical grounds: no pathognomonic laboratory or histological findings exist. The association of T2 hyperintense CNS lesions in the presence of oral and genital ulcers is the best diagnostic clue.

Blood Association to HLA-B51 may be present in severe cases.

CSF Abnormal in 70–80 % of parenchymal NB, with raised proteins in most cases.

MRI May show focal or diffuse lesions mostly in brainstem or basal ganglia to the diencephalon [19]. Lesions may be localized within the subcortical white matter and hypothalamic regions. Venous sinus thrombosis can be demonstrated by magnetic resonance and brain CT venography.

3.2.1.4 Prognosis

Therapy

In acute episodes of parenchymal NBD, corticosteroids (oral prednisolone: 1 mg/kg, or with high-dose intravenous methylprednisolone (1 g/day) for 3–7 days) have a short-lived effect and do not prevent further attacks or progression. Colchicine, azathioprine, cyclosporine-A, cyclophosphamide, methotrexate, chlorambucil, and immunomodulatory agents such as IFN-a, pentoxyphilline, and thalidomide have been anecdotally reported useful in treating some of the systemic manifestations of BS, but none of them are effective in NBD [16, 17].

Deep venous thrombosis in NBD requires anticoagulants and antiplatelet agents with intermediate doses of corticosteroids [17, 20].

Disability Most patients with an acute parenchymal inflammatory episode improve after steroid treatment. Retrospective series reported a mean of 20–30 % of patients with residual neurological impairments and 10 % mortality rate at 10 years [16, 20]. NBD is a significant cause of morbidity. Ten years after the onset of neurological deficits, 78.2 % of patients were found to develop at least mild (EDSS $\geq$3), and 45.1 % moderate to severe neurological disability (EDSS $\geq$6) [16]. On the contrary, patients affected by non-parenchymal NBD had minimal disability with EDSS scores of one or two.

About a third of patients had single episodes, a third had repeated relapses and remission, and a third underwent a progressive disease course with accrual of neurological impairments [16].

Adverse prognostic factors included: (a) progressive course, (b) frequent relapses, and (c) residual neurological impairments during remissions [20]. Patients with brainstem and spinal cord lesions recovered less well; elevated proteins and pleocytosis in the CSF were also associated with poorer prognosis [16].

Patients with silent neurological involvement tend to regress toward clinically evident deficits.

Appropriate treatment may improve and reduce the risk of recurrence of venous sinus thrombosis and intracranial hypertension.

3.2.2 Sarcoidosis

Key Facts

- **Terminology and definitions** – Sarcoidosis is a granulomatous disorder that affects multiple organs. Neurosarcoidosis affected 5 % of patients with sarcoidosis.
- **Clinical features** – Cranial neuropathies (from second to seventh cranial nerves), aseptic meningitis, seizures, hydrocephalus, and PNS deficits.
- **Diagnostic markers** – Based mostly on clinical findings.
  - **CSF** – Might show hypoglycorrhachia, mononuclear pleocytosis and high titer of angiotensin-converting enzyme. Biopsy might be helpful.
  - **MRI** – Leptomeningeal enhancement (particularly at the skull base) is typically present. Hypothalamus, infundibulum, and pituitary gland might also be involved.
- **Top differential diagnoses** – Tuberculosis, neoplasia, infectious meningitis, MS, SLE.
- **Prognosis** – PNS involvement carries good prognosis; CNS involvement often causes disability.
- **Principles of treatment** – Steroids and immunosuppressive drugs.

3.2.2.1 Terminology and Definitions

Sarcoidosis is a granulomatous disorder that affects multiple organs. Five percent of patients with sarcoidosis have nervous system localizations (neurosarcoidosis).

3.2.2.2 Demographics

Neurosarcoidosis (NS) more commonly occurs with other sarcoidosis forms; in 1 % of cases it involves only the nervous system.

3.2.2.3 Clinical Features

Cranial neuropathies are the most common manifestations of neurosarcoidosis (50–75 %), with facial nerve palsy being the most frequent symptom (25–50 %). Sarcoidosis-related optic neuritis is an emergency because permanent vision loss may occur [21]. Hydrocephalus has been described in 5–7 % of cases. Headache due to meningitis, encephalopathy, mass lesions, or hydrocephalus are further common manifestations. Fifteen percent of patients will develop seizures. Several neuropsychiatric conditions, including depression, and psychosis may be associated. Neuroendocrine dysfunctions may be caused by sarcoid granulomas of hypothalamic-hypophysial complex [21, 22].

3.2.2.4 Diagnostic Markers

CSF Angiotensin-converting enzyme may be elevated [23].

Biopsy Patients without known systemic sarcoidosis who develop a brain or spinal cord mass are usually biopsied for definitive diagnosis.

Imaging Leptomeningeal involvement at MRI is the most common finding of neurosarcoidosis [24, 25]. In addition, neurosarcoidosis may present as solitary or multiple enhancing intraparenchymal masses [25]. The pituitary gland, infundibulum, and hypothalamus are involved in 18 % of patients [25].

3.2.2.5 Therapy

No well-designed study delineates the optimal treatment of neurosarcoidosis. A goal of treatment is to diminish the irreversible fibrosis that can develop, as well as the tissue ischemia that might result from perivascular inflammation [26]. The inflammatory process may become quiescent with time.

Corticosteroids are the first-line treatment of sarcoidosis. In general, neurosarcoidosis is less responsive to corticosteroids than sarcoidosis of other body parts.

More than 70 % of patients treated with corticosteroids alone developed neurological deterioration. Immunomodulating and cytotoxic agents such as azathioprine, cyclophosphamide, or methotrexate have been shown to improve the neurological outcome in approximately one-fifth of cases of neurosarcoidosis refractory to corticosteroids [26, 27].

A combination of corticosteroids with either methotrexate, azathioprine, or cyclophosphamide has resulted in a favorable outcome in neurosarcoidosis patients with severe CNS involvement.

3.2.2.6 Prognosis

Long-term clinical outcome of neurosarcoidosis has rarely been evaluated.

Approximately two-thirds of patients have a monophasic neurological illness; the remainder display chronically progressive or a remitting–relapsing course. Whether treatment changes the natural history of the disease is not proven, though in the short-term symptoms can often be relieved by therapy [21, 24, 26].

Generally, PNS involvement has a more favorable clinical outcome than CNS localized disease. No correlation between extra-neurological manifestations and clinical outcome exist, suggesting that systemic involvement is not a predictive factor for the evolution of neurosarcoidosis. Optic nerve atrophy has bad prognosis. On the contrary, facial nerve palsies tend to have a good prognosis [21, 27, 28]. Hydrocephalus is a rare manifestation of sarcoidosis with poor long-term prognosis [27].

Spinal cord neurosarcoidosis occurs in <1 % of patient, but often causes severe neurological sequelae [28]. In general, people with cranial neuropathy (except optic neuropathy), acute meningitis, or peripheral neuropathy have a lower risk for progression and long-term disability than patients with intracranial disease.

Indeed, CNS involvement causes severe conditions and higher morbidity and mortality [27, 28]. Seizures and intense gadolinium enhancement are also linked to poor prognosis.

One-third of patients display refractory forms of NS with higher morbidity and mortality. Laboratory findings (including CSF and blood) do not predict refractory NS; in addition, the common markers of disease activity (blood and CSF ACE, gallium scintigraphy) do not correlate with clinical outcome [28].

3.2.3 Primary Sjögren Syndrome (PSS)

Key Facts

- **Terminology and definitions** – (Synonyms: Sicca syndrome, Gougerot-Sjögren syndrome). Autoimmune disease affecting exocrine glands and extraglandular organs including both PNS and CNS.
- **Clinical features** – Keratoconjunctivitis sicca and xerostomia are the typical findings [29]. Peripheral neuropathies are observed in 25 % of cases. Aseptic meningoencephalitis and psychiatric or cognitive symptoms are emblematic of CNS involvement.
- **Diagnostic markers**
  - **Blood** – Antibody against extractable RNA proteins Ro are found in Sjögren syndrome A (SS-A); antibody against intranuclear RNA-associated antigen La are found in Sjògren syndrome-B (SS-B).
  - **MRI** – Is the first choice examination for spinal cord lesion or deep and subcortical white matter alterations.
- **Top differential diagnoses** – Multiple sclerosis, neuromyelitis optica, SLE.
- **Prognosis** – Better outcome in patients with PNS than CNS involvement.
- **Principles of treatment** – Steroids and immunosuppressive drugs.

3.2.3.1 Clinical Features

More than 90 % of people affected by Sjögren's (0.5–1 % of the population in USA) syndrome are women. The disease is most often seen in the sixth decade of life. The prevalence of its neurological manifestations (more often of CNS than PNS) varies between 10 and 60 % of all PSS.

CNS deficits are characterized by affective and personality disorders, frontal lobe abnormalities, mild cognitive dysfunction, and aseptic meningitis [30, 31].

3.2.3.2 Diagnostic Markers

Blood Ab anti Ro (SSA form) and La (SSB form) autoantigens represent a diagnostic tool PSS. Antinuclear antibodies (ANA) are present in 59–85 % of patients. Cryoglobulins, rheumatoid factor, and alpha-fodrin positivity have been also described [32].

CSF Aseptic meningitis, increased IgG, and oligoclonal bands can be found in CNS involvement.

Biopsy Nerve, muscle, or skin biopsy may confirm the presence of secondary vasculitis.

Imaging MRI may show CNS involvement similar to that of MS. Spinal cord can show T2 abnormalities in the posterior columns caused by neuronopathy [31, 32].

EMG/ENG May demonstrate PNS sufferance.

3.2.3.3 Therapy

Based on the incomplete data available, it appears that corticosteroids are often effective in PSS-associated multiple mononeuropathy and multiple cranial neuropathy [30, 32], but not in sensory ataxic neuropathy.

Some AA suggest the doubtful efficacy of IVIg therapy in PSS-associated sensory ataxic neuropathy and small fibers neuropathy [33]. Cyclophosphamide can be a second choice treatment.

Infliximab (chimeric human-mouse anti-tumor necrosis factor-alpha antibodies) may be of some utility in CNS disease [30, 32].

3.2.3.4 Prognosis

In most cases, PSS is a chronic, slow-evolving disease characterized by sicca symptoms, widespread pain, and fatigue. Some patients experience severe and sometimes life-threatening extraglandular manifestations such as peripheral or central neuropathy, interstitial lung disease, polysynovitis, tubular kidney disease, and cryoglobulinemic vasculitis. These manifestations may require steroids and immunosuppressants, and the definition of "at-risk" patients is paramount. The worst concern in patients with pSS is the development of lymphoma (10 % of patients).

Outcome is good in patients with PNS involvement. Patients with spinal cord injuries have a more severe disability. Anti-Ro (SS-A) positivity has been associated with more severe CNS disease and abnormal angiographic findings [32, 34].

3.2.4 Systemic Lupus Erythematosus (SLE)

Key Facts

- **Terminology and definitions** – SLE is an autoimmune disease that may affect many internal organs. The neural manifestation of lupus is known as neuropsychiatric SLE (NP-SLE).
- **Clinical features** – Cognitive dysfunction, headache, cerebrovascular disease, and seizures are the most frequent of its manifestations.
- **Diagnostic markers** – Based on clinical findings, four criteria of the 11 stated by the American College of Rheumatology are necessary for the diagnosis of SLE.
  - **Blood** – Autoantibodies are useful for SLE diagnosis; there are no specific laboratory biomarkers for NP-SLE.
  - **MRI** – Typical findings are multiple white matter lesions on T2 imaging. Atrophy, infarcts, hemorrhages, venous thrombosis, cerebral abscess, and myelitis are also described.
- **Top differential diagnoses** – MS, sarcoidosis, other autoimmune diseases.
- **Principles of treatment** – Steroids and immunosuppressive therapy are helpful. Anticoagulants are useful in patients with positivity of antiphospholipid antibodies.
- **Prognosis** – Neurological involvement and renal impairment due to SLE tend to be correlated with poor prognosis. Neuropsychiatric events during the acute phase of SLE and early stage of disease (SLE-related form) are not associated with a prognosis poorer than non NP-SLE syndromes.

3.2.4.1 Neuropsychiatric SLE

Demographics

The prevalence of CNS involvement in patients with SLE is 50 %, with a wide range (from 14 to 75 %) due to the lack of standardized definitions and to the predominance of retrospective studies.

Clinical Features

Nineteen different neurological manifestations are described in SLE patients [35]. Cognitive dysfunction and headache are frequent. Ischemic stroke due to thrombosis, hypertension, and vasculitides is a common manifestation in SLE patients with a history of cerebrovascular disease.

Epilepsy and acute confusional state are further manifestations. SLE myelopathy occurring as fast evolving transverse myelitis or ischemic/thrombotic myelopathy can also occur.

Psychosis is the main feature of psychiatric SLE [35, 36].

Diagnostic Markers

Most (50–60 %) SLE-related events occur at disease onset or within the first 1–2 years. Neurological deficits occurring more than 6 months before the onset of SLE are less likely [36]. NP events in patients with SLE are of variable frequency, most commonly present early in the disease course and adversely impact on quality of life.

Blood The presence of autoantibodies in serum is a diagnostic criteria. No diagnostic biomarkers exist for NP-SLE patients. The occurrence of antiphospholipid antibodies plays a key role in the therapeutic decision [36].

MRI abnormalities are seen in 54–81 % of patients with NP-SLE and in 15–50 % of patients without neuropsychiatric manifestations. MRI also provides a volumetric assessment of brain atrophy [37]. Neuropsychiatric symptoms in patients with SLE may be related to metabolic and/or functional alterations caused by the disease; they usually antedate the development of MRI abnormalities [38].

Therapy

Immunosuppression is the cornerstone of the management of NP-SLE and can be obtained by high-dose glucocorticoids, cyclophosphamide, or azathioprine. Although the number of studies is small, there is convincing evidence that oral or intravenous glucocorticoid therapy is beneficial [36].

Plasmapheresis is an adjunctive treatment in patients with severe and progressive NP-SLE.

Anticoagulation may be superior to antiplatelet therapy for secondary prevention of arterial events in antiphospholipid antibody syndrome (APS).

Prognosis

Neuropsychiatric syndromes strongly influence the short-term disease-related and health-related outcomes in patients with SLE, regardless of specific etiology. NP events in SLE have been associated with increased organ damage, fatigue, unemployment, and lower quality of life [39]. Specific NP syndromes, such as cerebrovascular disease and myelopathy, have been associated with an increased rate of mortality. Kidney and neuropsychiatric damage negatively affects survival [40]. Early detection and aggressive management of renal and neuropsychiatric involvement may potentially improve the survival of lupus patients.

Patients with IgG anticardiolipin antibodies experienced faster reductions in psychomotor promptness compared to other patients. Patients with IgA anticardiolipin antibodies performed less well on reasoning and skills tasks.

Major events such as cerebrovascular involvement, severe cognitive dysfunction, myelopathy, and optic neuritis often result in significant morbidity and poor functional outcomes [41, 42]. NP deficits adversely affect patients' quality of life; neurological injuries due to non-SLE causes are more common than syndromes due to SLE and have a less positive outcome [41].

The long-term prognosis and patterns of disease in SLE patients with early NP events are similar to those of SLE patients without these events [42].

3.2.5 Giant Cell/Horton Arteritis (GCA)

Key Facts

- **Terminology and definitions** – Giant cell/Horton arteritis is a systemic inflammatory vasculitis of unknown etiology.
- **Clinical features** – New-onset headache with fatigue, anorexia, and weight loss in patients older than 50 years. Vision loss is the most feared danger.
- **Diagnostic markers**
  - **Laboratory**
    - **Blood** – Increased erythrocyte sedimentation rate, C-reactive protein, and platelet count.
    - **Temporal artery biopsy** – Sensitivity of 24–90 %, specificity of 81–100 %.
    - **Imaging** – *Doppler ultrasound* flow may show the "dark halo sign"; *high resolution MRI* is useful.
- **Top differential diagnoses** – Migraine, glaucoma, Takayasu arteritis, uveitis.
- **Prognosis**
  - **Principles of treatment** – Prompt treatment with steroids.
  - **Disability** – GCA is a medical emergency with an extremely poor prognosis, if untreated. Permanent visual deficits, occasionally bilateral amaurosis, may occur in 20 % of patients. Steroids may not stop GCA progression.

3.2.5.1 Terminology and Definitions

Giant cell arteritis (GCA) (also known as temporal arteritis, Horton arteritis) is a systemic inflammatory vasculitis of unknown etiology.

3.2.5.2 Epidemiology

GCA is the most common form of systemic vasculitis in adults and usually involves branches of the internal and external carotid arteries (superficial temporal arteries, in particular). Its median age of onset is 75 years with incidence of 0.5/27 per 100,000 in people aged or older than 50 years. The female/male ratio is 3.7/1.

Ten to twenty percent of patients with polymyalgia rheumatica develop temporal arteritis.

3.2.5.3 Clinical Features

The classic presentation includes new-onset headache with fatigue, anorexia, and weight loss in patients older than 50 years. Temporal arteries are usually involved and may be enflamed, swollen, and painful. Jaw claudication is highly frequent. Vision loss is the most feared danger.

3.2.5.4 Diagnostic Markers

Blood Increased erythrocyte sedimentation rate (mean values 93 ± 23 mm/h), C-reactive protein (mean value 94 ± 63 mg/L), and platelet count.

Temporal Artery Biopsy With a sensitivity of 24–90 % and specificity of 81–100 % is gold standard for diagnosis, but can be substituted by imaging, and avoided in typical cases.

Pathology Aspects of necrotizing arteritis with multinucleated giant cells characterize the picture.

Imaging Doppler ultrasound flow detector showing the "dark halo sign" in typical cases, with a specificity of 90 % is commonly used.

High Resolution MRI May confirm the diagnosis; negative MRI would not be sufficient to rule out GCA.

3.2.5.5 Top Differential Diagnosis

Migraine, glaucoma, Takayasu arteritis, uveitis.

3.2.5.6 Therapy

GCA is a medical emergency. Prompt treatment with steroids may prevent blindness. Prednisone (50–60 mg/day for about 1 month and then gradually tapered) and high-dose methylprednisolone are the treatments of choice at onset. The average duration of treatment with steroids is 2 years; however, some patients require treatment for 5 years or more. Antiplatelet drugs (aspirin 100 mg/day) decrease the ischemic complication rate. Cyclosporine and azathioprine may be employed as steroid-sparing drugs. Methotrexate has been suggested for high-risk patients. Relapses are frequent.

3.2.5.7 Prognosis

If untreated, the prognosis of GCA is extremely poor. The greatest risk of visual deterioration is in the first 6 days. Recovery of visual deficits is also meager, and permanent visual deficits, occasionally bilateral amaurosis, may occur in 20 % of patients.

Corticosteroid therapy improves the visual prognosis in temporal arteritis, but may not stop its progression.

Patients with visual loss had a mean visual acuity of 20/400. The greatest risk of visual deterioration was in the first 6 days. Visual deterioration occurred in 27 % of eyes within the first week, despite high-dose IV corticosteroids. Only fifteen percent of eyes showed an improvement of visual acuity within the first month [43].

GCA is associated with increased danger of stroke and peripheral vascular disease. The hazard ratios were 2.06 for myocardial infarction, 1.28 for stroke, and 2.13 for peripheral vascular disease. Hazard ratios were more pronounced in the first month after its diagnosis. Long-term complications of giant cell arteritis are high, but mortality rates remain the same as in control groups,

Only anemia was found to be a negative predictor for the development of severe ischemic manifestations of GCA (odds ratio, 0.53; 95 % confidence intervals, 0.30–0.94; $p = 0.03$) [44].

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Trauma of the Central Nervous System

4

Marco Gemma and Maria Rosa Calvi

4.1 Traumatic Brain Injury

Key Facts

- **Terminology and definitions** – Traumatic brain injury (TBI) is an alteration of brain function caused by external mechanical forces.
- **Clinical features** – Neurological deficits (motor, sensitive, cognitive, etc.) depend on the anatomical sites involved. Severity of trauma: mild 12 < GCS, moderate 9 ≤ GCS ≤ 12, severe GCS < 9.
- **Diagnostic markers**
  - **Imaging** – On admission and then repeated when useful.
- **Top Differential Diagnoses** – Traumatic event may be secondary to other acute diseases.
- **Prognosis**
  - **Principles of treatment** – Treatment protocols are devoted to limiting secondary brain injury after TBI.
  - **Prognosis** – IMPACT, CRASH prognostic calculators. Negative prognostic factors are: older age, impairment of consciousness, low GCS score, bilaterally absent pupillary light reflex, arterial hypotension and hypoxia, occurrence of any TBI-related abnormality on neuroimaging, and intracranial hematomas.

  Mortality of severe TBI is 25 %. Mild TBI: only two variables predict poor outcome: (1) age, (2) presence of extracranial injuries.

Abbreviations

AEH, *A*cute epidural hematoma; ARDS, *A*dult respiratory distress syndrome; AIS, *ASIA* Impairment Scale; ASH, Acute subdural hematoma; BTF, *B*rain Trauma Foundation; CPP, *C*erebral perfusion pressure; CRASH, *C*orticosteroid Randomization after Significant Head Injury; DAI, *D*iffuse axonal injury; DTI, *D*iffusion tensor imaging; EEG, Electroencephalogram; FIM, *F*unctional independence measure; FOUR, *F*ull Outline of UnResponsiveness Scale; GCS, *G*lasgow Coma Scale score; GOS, *G*lasgow Outcome Scale; GOS-E, *E*xtended GOS; ICP, *I*ntracranial pressure; ICU, *I*ntensive care unit; IMPACT, *I*nternational Mission for Prognosis and Clinical Trials in Traumatic Brain Injury; ASIA, *I*nternational Standard Committee of the American Spinal Injury Association; ISNCSCI *I*nternational Standards for Neurological Classification of Spinal Cord Injury; MAP, *M*ean arterial pressure; $PbtO_2$, *B*rain tissue oxygen; PTA, Posttraumatic amnesia; SCI, *T*raumatic spinal cord injury; SH, *S*ubdural hematoma; TBI, *T*raumatic brain injury; Traumatic subarachnoid hemorrhage (tSAH)

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4.1.1 Terminology and Definitions

Traumatic brain injury (TBI) is an alteration of brain function caused by external mechanical forces.

These forces may penetrate the skull (penetrating TBI) or leave it intact (blunt TBI).

Damage can be produced by forces directly hitting the head or by indirect acceleration/deceleration or blast waves.

TBI causes different brain lesions:

- Acute epidural hematoma (AEH)
- Subdural hematoma: acute (ASH) or chronic
- Intraparenchymal lesion
  - Intraparenchymal hematoma
  - Contusion
  - Infarction
  - Delayed traumatic intracerebral hematoma
- Diffuse lesion
  - Brain swelling
  - Diffuse axonal injury (DAI)
  - Traumatic subarachnoid hemorrhage (tSAH)

In particular, DAI typically occurs during high-speed impact trauma causing rotational acceleration.

Given the high sensitivity of the brain to hypoxia, besides direct injury occurring at the moment of trauma, brain tissue impairment following TBI is largely caused by secondary brain injury. This term indicates the ominous effects of metabolic/perfusion uncoupling following TBI. High intracranial pressure (ICP), low cerebral perfusion pressure (CPP), and brain tissue metabolism alterations play a central role in the pathophysiology of secondary brain injury.

Epidemiology With an estimated annual incidence of up to 500 cases per 100,000 population in the USA and Europe, TBI is the leading cause of death and disability among young adults and its incidence in the elderly population is increasing.

High-speed-related injury due to traffic accident is the most frequent cause of TBI in young people, while TBI in older people is more often related to falls.

Males are affected twice as much as females.

4.1.2 Clinical Features

Direct injury to the brain causes neurological (motor, sensitive, cognitive, etc.) deficits depending on the anatomical sites involved.

Moreover, TBI is often associated with other lesions (spinal, visceral, etc.) that may significantly affect patients' conditions. Treatment priorities have to be determined by taking into account survival. Further considerations regarding quality of life after TBI should be postponed until adequate treatment of associated life-threatening conditions.

It should be noted that TBI does not produce hemodynamic impairment, and extracranial causes of shock (if present) should be aggressively searched for and treated. Elevated intracranial pressure may produce bradycardia, hypertension, and irregular breathing (Cushing response).

Spinal and particularly cervical spinal injuries must be ruled out in any TBI case.

The most prominent sign after TBI is the impairment of consciousness and TBI is traditionally classified according to the Glasgow Coma Scale (GCS) score (Sect. 4.5.1.2.1 below and Table 4.1) as:

- Mild $12 < GCS$
- Moderate $9 \leq GCS \leq 12$
- Severe $GCS < 9$

Patients may be found unconscious from the time of injury, a typical occurrence in DAI, or may present a "lucid interval" between trauma and loss of consciousness (patients that "talk and die").

This lucid interval is poorly defined and does not seem to be related to prognosis. It typically occurs in epidural or subdural hematomas.

Patients with severe TBI require intensive care unit (ICU) admission.

4.1.3 Diagnostic Markers

- History
- Clinical examination
  - Neurological
    - Glasgow Coma Scale
    - Pupils
  - General
    - Ventilation
    - Hemodynamics
- CT scan (on admission and then repeated according to guidelines)
- ICP monitoring (if indicated)
- Brain oxygen monitoring (if indicated)
  - Jugular vein O_2 saturation
  - Brian tissue O_2 saturation
- Electroencephalogram (EEG)

4.1.4 Top Differential Diagnosis

The traumatic event and its temporal correlation with typical posttraumatic lesions usually excludes any differential diagnosis.

Nevertheless, sometimes the traumatic event may be secondary to other acute diseases. Patients suffering acute impairment of consciousness from neurological (e.g., stroke or epileptic seizure), cardiac (e.g., myocardial infarction or arrhythmias), or toxic/metabolic causes may fall or be involved in various types of accidents leading to TBI.

This issue is not only significant on a legal basis, but deserves clinical attention, since concomitant diseases may exert an important role in patient management.

In dealing with TBI patients, suspicion of possible causative (or at least favoring) acute diseases should arise on the basis of:

- Patient history (e.g., presence of epilepsy or heart disease)
- TBI history from witnesses

Table 4.1 Glasgow Coma Scale (GCS)

	Points	Description
Best motor response	1	No movement
	2	Extensor response (decerebrate): elbow extension with pronation and adduction (to local painful stimulus, sometimes spontaneously)
	3	Abnormal flexion (decorticate): slow withdrawal with wrist pronation, shoulder adduction (to local painful stimulus, sometimes spontaneously)
	4	Withdraws: normal flexion of elbow or knee to local painful stimulus
	5	Localizes: other limb moves to site of painful stimulation
	6	Obeys commands (exclude grasp reflex or postural adjustments)
Verbal response	1	None
	2	Incomprehensible speech (moans and groans only – no words)
	3	Inappropriate words (intelligible words but mostly expletives or random)
	4	Confused conversation (attends and responds but answers muddled/wrong)
	5	Orientated (knows who, where, when; year, season, month)
Eye opening	1	None
	2	To pain applied to limbs (not face, where grimacing can cause closure)
	3	To speech when spoken to (not necessarily the command to open eyes)
	4	Spontaneous (indicates arousal, not necessarily awareness)

- Neuroimaging (e.g., intraparenchymal or subarachnoid hemorrhage suggesting intracranial spontaneous bleeding)

The differential diagnosis between accidental and postaggression TBI is a legal issue that goes beyond the scope of this review.

However, clinicians should be trained to recognize child abuse as a particular postaggression TBI.

It should be noted that magnetic resonance evidence of recurrent subdural hematomas in children are highly suggestive of the "shaken baby syndrome."

Patients affected by cognitive or sensory-motor diseases may undergo TBI with increased frequency. Differentiating previous and ongoing disease may be challenging.

4.1.5 Prognosis

Major efforts have been made to establish prognostic criteria for severe TBI.

This is motivated not only by the high incidence of severe TBI in young people but also by the compelling need to streamline resource allocation.

Although it is not always formally justified, conclusions about severe TBI prognosis are commonly extended to moderate TBI, while mild TBI is considered separately.

Assessment of TBI outcome is usually quantified by means of the Glasgow Outcome Scale (GOS) (Table 4.2) [1].

In order to simplify the outcome assessment, GOS is often dichotomized into two classes of outcome:

1. "Good outcome" (or "favorable outcome") encompassing good recovery and moderate disability
2. "Poor outcome" (or "unfavorable outcome") encompassing death, vegetative state, and severe disability

Although statistically inefficient [2], this dichotomization simplifies statistical analysis and clinical information and is the most widespread tool for TBI outcome assessment.

As an opposite trend, the Extended GOS (GOS-E: Table 4.2), with its 8-level score ranging from 1 to 8 (Dead to Upper Good Recovery), offers an improvement in sensitivity and is increasingly used in the research setting [3].

Patients may theoretically be scored with GOS at any time after trauma, but GOS is specifically validated on a time span of 6 months after trauma and this is currently considered the most correct timing of GOS scoring.

Table 4.2 Glasgow Outcome Scale (GOS)

GOS		GOS-E		
Death	Death within a specified time from trauma	Death within a specified time from trauma		Poor outcome
Vegetative	Unawareness with only reflex responses but with periods of spontaneous eye opening	Unawareness with only reflex responses but with periods of spontaneous eye opening		
Severe disability	Conscious but dependent for daily support from another person by reason of mental or physical disability	Low severe disability	Cannot be left alone for more than 8 h at home	
		Upper severe disability	Can be left alone for more than 8 h at home	
Moderate disability	Some disability (e.g., dysphasia, hemiparesis, epilepsy, deficits of memory or personality) but able to look after themselves, do shopping and travel by public transport	Low moderate disability	Unable to return to work even with special arrangement	Good outcome
		Upper moderate disability	Able to return to work even with special arrangement	
Good recovery	Resumption of normal life with the capacity to work (preinjury status not necessarily achieved) – neurological or psychological deficits possible	Low good recovery	With disabling deficits	
		Upper good recovery	Without disabling deficits	

4.1.5.1 Moderate and Severe TBI Prognosis

Several single TBI prognostic variables have been outlined and their predictivity has been extensively scrutinized [4].

A major resource for a comprehensive literature review on single predictors is the Brain Trauma Foundation (BTF) guideline collection, available online and updated on a regular basis [5].

Past attempts to define TBI prognosis examined single variables with a univariate approach.

Recently, a new approach of multivariate logistic predictive models combining various predictors of outcome has crossed over from scientific research into the clinical setting.

This approach has radically changed the attitude towards prognostic variables.

As evidence grew that the severity of TBI outcome is actually multifactorial, attempts were made to build multivariate predictive models of outcome after TBI.

Two prediction models are particularly important with regard to this: the International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury (IMPACT) prognosis calculator [6, 7] and the Corticosteroid Randomization after Significant Head Injury (CRASH) prognosis calculator [8]. These models underwent both accurate internal calibration and extensive external validation, and also discriminate outcomes with areas under the receiver operating characteristic curve (AUROC) in the range of 0.6–0.8. In particular, the IMPACT calculator represents the most evolved prognostic tool for moderate and severe TBI available at present.

It combines covariate adjustment together with ordinal logistic regression and explores the possibility of nonlinearity for regression variables.

IMPACT is validated for patients with a GCS $\leq$12 on admission (after stabilization of systemic conditions) and yields the probability of death and of poor outcome 6 months after trauma, taking into account ten predictive variables recorded on admission. These variables generate three models with increasing complexity.

- The core model includes age, GCS motor score, and pupil reactivity to light. It yields most of the prognostic information of IMPACT.
- The extended model also includes the occurrence of hypoxia, hypotension, posttraumatic subarachnoid hemorrhage, epidural hematoma, and Marshall's Traumatic Coma Data Bank CT scan classification.
- The laboratory model also includes serum glucose and blood hemoglobin.

A major interest of the IMPACT enterprise lies in the modern methodology it exploits [2] in analyzing the heterogeneity among patients regarding causes, pathophysiology, treatment, and outcome.

Neither the CRASH nor the IMPACT prognosis calculator takes the treatment protocol into account. This could be a critical issue and some evidence suggests that both calculators actually overestimate the frequency of death and poor outcome in patients treated according to the Lund concept [9, 10].

A second limitation of CRASH and IMPACT is that they address predictors that were suggested by previous studies: it is possible that other relevant predictors need to be included in multivariate models.

A third limitation of these models is that they produce baseline prognosis and cannot be employed for dynamic predictions that take into account conditions and events occurring over the course of the disease process.

Mathematical interpretation of single predictive variables has to be put into perspective and no single predictor can now be considered outside the framework of the proposed multivariate logistic predictive models.

Nevertheless, an account of relevant or potential predictors of TBI prognosis is reported below.

Age

Age is a strong independent predictive factor for poor outcome after severe TBI, with a minimum 70 % positive predictive value for poor outcome when considered in univariate analysis.

The probability of poor outcome increases with increasing age. This relationship is nonlinear and there is some debate about the relevant coefficients, especially in the pediatric age.

Some characteristics of increased age may account for this relationship, particularly the decline in baseline health conditions with a higher incidence of preexisting disease, and a general decreased capacity for functional repair of the brain. These factors have not yet been clearly identified.

However, it has been demonstrated that the age effect on outcome is not explained by the increased frequency of systemic complications or intracerebral hematomas with age.

Impairment of Consciousness

Impairment of consciousness is conceivably the most impressive effect of trauma on the brain.

The severity of this impairment intuitively marks the severity of TBI and the clinical evaluation of it provides important clues to the prognosis after TBI.

The Glasgow Coma Scale (GCS)

The GCS (Table 4.1) was originally developed [11] for the repeated intrahospital assessment of consciousness over time after TBI, but its use has gone far beyond this scope and it is frequently applied to evaluate impaired consciousness regardless of its causes.

This extension of the GCS beyond its original scope has not always been adequately validated but it stemmed from the good performance of GCS in assessing consciousness after TBI.

To this end, its most important result is the continuous relationship found between mortality and the score across the entire range of GCS score [12]. It yields a more than 70 % positive predictive value for poor outcome when considered in univariate analysis.

Criticism of the GCS arose early and has increased sharply in the last few years:

- The temptation to add up the three GCS items in a single "total" GCS score leads to the widespread use of a "total" GCS. This produces loss of information and is mathematically unsound, since the items differ in their respective prognostic importance and different weights should be attributed to them. In fact, different permutations of item scores with a same "total" GCS have actually different prognostic significance.

  Although the "total" GCS is deeply rooted in clinical practice, GCS should always be reported with its three separate items.
- Inter- and intraobserver reproducibility may be low, particularly in differentiating GCS motor score 3 and 4.
- GCS does not provide a complete clinical assessment, since it does not address some important features (e.g., brain stem impairment), so it is evident that prognosis cannot rely exclusively upon GCS evaluation.
- GCS is affected by several conditions other than the severity of injury. Toxic and metabolic causes of coma, suboptimal respiratory or hemodynamic conditions, sedation, and muscle paralysis lead to underestimation of GCS. These factors should be evaluated and possibly removed before scoring patients with the GCS. The very evaluation of some GCS items is impaired by several conditions, such as tracheal intubation, facial trauma, spinal injury, and preexisting disease.

Other Scales

Due to the aforementioned criticism about GCS, other scales gained some degree of popularity after demonstration that they are at least as predictive of TBI outcome as the GCS. They are usually designed to evaluate impaired consciousness of any cause.

Some scales are more complex than the GCS, since they aim at providing a more thorough evaluation of TBI. The FOUR (Full Outline of UnResponsiveness) scale is a typical example [13]: it consists of four components (eye, motor, brainstem, and respiration evaluation).

Other scales are simpler than the GCS and aim at providing easier-to-use instruments that avoid some of the GCS pitfalls. Distinctive examples of these are the AVPU scale [14], the ACDU scale [14], and the Simplified Motor Scale [15] (Table 4.3).

Table 4.3 Three commonly proposed simpler alternatives to the Glasgow Coma Scale (GCS)

Simplified Motor Scale	Obeys commands
	Localizes pain
	Withdrawal to pain or less response
AVPU scale	Alert
	Responds to vocal stimuli
	Responds to painful stimuli
	Unresponsive to any stimulus
ACDU scale	Alert
	Confused
	Drowsy
	Unresponsive

Although theoretically interesting, these scales are not extensively used.

Pupil Evaluation

Damage to the midbrain third nucleus or to the efferent third cranial nerve by temporal lobe compression produces "fixed" pupils, i.e., the pupillary light reflex is absent (pupillary diameter reduces <1 mm after exposure to bright light). Usually pupils are also dilated (>4 mm).

A bilaterally absent pupillary light reflex is a strong predictor of poor outcome, with a more than 70 % positive predictive value of poor outcome in univariate analysis.

Pupil evaluation has good intra- and interobserver reliability, but direct third nerve injury can also lead to dilated or fixed pupils and confound neurological evaluation.

Moreover, suboptimal respiratory and hemodynamic conditions may affect pupil evaluation and hypotensive or hypoxemic patients may even exhibit fixed dilated pupils that return to normal after proper resuscitation.

Other pupillary signs, namely asymmetry in pupillary size (>1 mm) or light reflex, are not independent predictors of outcome, although they are very important in guiding therapy.

Arterial Hypotension and Hypoxia

The occurrence of a systolic blood pressure of less than 90 mmHg has a 67 % positive predictive value for poor outcome, and increases to 79 % if hypotension is associated with hypoxia, when analyzed with univariate analysis.

This variable has been studied particularly during the prehospital and early phases after TBI.

In fact, hypotension is a typical example of the usefulness of nonlinear regression evaluation employed in modern multivariate prognostic models. The relationship between systolic blood pressure and outcome is U-shaped, so that very low and very high systolic blood pressure on admission yield a similar probability of poor outcome.

The effect of hypotension and hypoxia on the outcome of severe TBI is unique, since they are causes of poor outcome and not merely severity indicators. This makes them particularly interesting for two reasons.

From a pragmatic point of view, hypotension and hypoxia are strong predictors of outcome that are treatable and sometimes preventable.

From a theoretical point of view, their importance is related to the concept of secondary brain injury.

Neuroimaging

The occurrence of any TBI-related abnormality on CT scan is predictive of poor outcome.

Significant posttraumatic brain lesions may develop over time and early CT scans may be unreliable. CT scans obtained less than 6 h after trauma mandate a new CT examination after 6–8 h as 40 % of patients with a negative CT scan at admission develop CT abnormalities thereafter.

Various classifications of post-TBI CT scan imaging have been proposed, but Marshall's Traumatic Coma Data Bank CT scan classification is the most widely used due to its prognostic value (Table 4.4).

Among the various specific CT abnormalities, basal (perimesencephalic) cisterns compression, traumatic subarachnoid hemorrhage (tSAH), and midline shift are known to have a >70 % positive predictive value for a poor outcome in high quality studies [5].

Basal cisterns compression is considered an indirect index of high ICP (actually it is associated with a threefold probability of high ICP) and is associated with a low GCS score, lack of pupillary reactivity, and occurrence of hypotension/

hypoxia. Higher degrees of compression, that may become complete obliteration, are more strongly correlated with poor outcome.

The occurrence of tSAH is a strong independent predictive factor for poor outcome and the extent of tSAH is related to outcome. The Fisher's grading system for nontraumatic SAH is also usually applied for grading tSAH (Table 4.5).

Between 26 and 53 % of severe TBI patients exhibit tSAH and the presence of tSAH doubles the risk of death, carrying a positive predictive value of poor outcome of approximately 70 %.

Midline shift at the level of the septum pellucidum is less reliable as a predictor of outcome. In fact, it is influenced by the occurrence of bilateral lesions and by the effect of posttraumatic space-occupying lesions, which may be evacuated. Usually midline shift is considered clinically significant if >5 mm.

Table 4.4 Marshall's Traumatic Coma Data Bank classification of post-TBI CT scan imaging

Diffuse injury	I	Normal CT scan for age and preinjury status
	II	Cisterns present 0–5 mm midline shift present No high- or mixed-density lesion > 25 mL (May include bone fragments and foreign bodies)
	III (swelling)	Cisterns compressed or absent 0–5 mm midline shift No high- or mixed-density lesion >25 mL
	IV (shift)	Midline shift >5 mm No high- or mixed-density lesion >25 mL
Evacuated mass lesion		Any lesion surgically evacuated
Nonevacuated mass lesion		High- or mixed-density lesion >25 mL not surgically evacuated

Besides CT scan, which remains the examination of choice in the early phases of TBI and for repeated evaluation over time, magnetic resonance imaging (MR) has a role in the workup of TBI patients.

Diffusion tensor imaging (DTI), which is highly sensitive to white matter damage, has been suggested as a possible adjunctive variable to improve the IMPACT score accuracy [16].

The MR prognostic value after TBI is highlighted in DAI patients.

Patients exhibiting minor lesions or even no lesion on CT scan, which does not account for the severity of their clinical picture ("incongruous" CT), typically present MR lesions accounting for their conditions: CT scan can offer some clues to diagnosis [17], but it is at least inaccurate in identifying injuries.

In these patients, the involvement of the white-gray matter junction indicates stage I DAI, corpus callosum involvement indicates stage II DAI, and brain stem involvement indicates stage III DAI. Higher DAI stages are clinically more severe and prognosis is therefore poorer. The prognostic value of these stages has been included in multivariate prognostic models [18].

Intracranial Hematomas

Following TBI, acute epidural hematoma (AEH) is associated with around 10 % mortality rate, while acute subdural hematoma (ASH) mortality rate lies between 40 and 60 %.

ASH is an expression of the involvement of more violent forces in the TBI mechanism. For this reason, ASHs are mostly associated with

Table 4.5 Fisher's grading scale for subarachnoid hemorrhage on CT scan

Grade	CT scan appearance
1	No blood visualized
2	Diffuse deposition or thin layer with all vertical layers of blood (interhemispheric fissure, insular cistern, ambient cistern) <1 mm thick
3	Localized clots and/or vertical layers of blood 1 mm or greater in thickness
4	Diffuse or no subarachnoid blood, but with intracerebral or intraventricular clots

other intra- and extracranial lesions, while AEHs are not. Other intracranial lesions are found in 60–70 % ASHs and in 30–50 % of AEHs.

The outcome predictive variables described in the paragraphs above have a lower predictive strength in AEH than in ASH patients.

Surgical evacuation of AEH and ASH according to international guidelines [5] is crucial. It is common knowledge that an AEH prognosis may change from impending death to full recovery with appropriate surgical evacuation.

Intraparenchymal posttraumatic lesions are associated with poor outcome. The extension of intraparenchymal lesions is an expression of devastating brain tissue derangement and is inversely proportional to functional recovery. Moreover, certain intraparenchymal lesion locations are associated with poorer prognosis, with the posterior fossa being the most ominous location.

Nevertheless, the heterogeneity and evolving nature of intraparenchymal lesions preclude a clear-cut determination of their prognostic value. In any case, evidence supports the need for strict control of intraparenchymal lesions over time and prompt surgical treatment of them when needed. The mortality rate of delayed intraparenchymal lesions is between 16 and 72 %, largely dependent upon adequate surgical evacuation according to guidelines [5].

Laboratory

After TBI, routine laboratory analysis may offer clues to the diagnosis of co-morbidity.

Co-morbidities, such as renal or hepatic failure, exert an evident prognostic effect on mortality and morbidity in ICU patients and are relevant variables in any ICU severity score.

Two routine laboratory analyses directly affect TBI prognosis and are included in multivariate outcome predictive models, namely serum hemoglobin and glucose.

The high sensitivity of brain tissue to low levels of oxygen accounts for the poor outcome predictivity of low hemoglobin levels.

Serum glucose exhibits a U-shaped relationship with outcome. This nonlinear relationship indicates that both very low and high levels of serum glucose predict poor outcome.

The overall adverse effect of high glycemia in ICU patients (not necessarily acute brain damage patients) is a matter of debate and the benefit of lowering it is a currently popular topic in ICU scientific literature.

Brain Injury Biomarkers

Brain injury biomarkers are substances detected in cerebrospinal fluid (CSF) or blood after TBI and thought to be largely expressed in brain parenchyma.

Although several of these biomarkers have been identified and studied with respect to prognosis, none of them has been demonstrated to clearly predict outcome after severe TBI. Correlations with outcome has nevertheless been observed for some biomarkers and it is possible that future studies could identify a panel of them that could help assess prognosis.

Genetics

There is evidence that the APOE ε4 allele, which is linked to Alzheimer's disease, makes poor outcome twice as likely in TBI patients. It not only favors posttraumatic dementia, but also prolongs coma, increases the size of intraparenchymal hematomas, and even favors the occurrence of posttraumatic seizures.

Treatment

Treatment protocols are devoted to limiting secondary brain injury after TBI.

Although TBI treatment international guidelines are available and regularly updated [5] and adherence to these guidelines has reduced severe TBI mortality from 50–35 to 25 % or lower over the last 30 years, few evidence-based data are available regarding this topic.

When dealing with different treatment strategies, the following issues are particularly relevant to prognosis.

ICP/CPP Targeted Treatment

Maintenance of ICP <20 mmHg is a cornerstone of TBI management worldwide and has been

suggested as useful in every edition of the international guidelines for TBI treatment [5], although evidence of its efficacy in randomized, controlled trials is still lacking.

Based on imaging and clinical examination in a multicenter, controlled trial [19], ICP targeted therapy was not shown to be superior to care. However, ICP control continues to be practiced in modern ICUs because of its strong rationale and experimental evidence.

Previous guidelines suggested the maintenance of CPP >70 mmHg to reduce secondary brain injury. Present evidence indicates that CPP >50 mmHg reduces secondary brain injury, but efforts to elevate CPP >70 mmHg should be avoided, since this increases the incidence of adult respiratory distress syndrome (ARDS).

However, the question of what is the optimal CPP to maintain after TBI remains unanswered.

Brain Tissue Oxygen

Given the high sensitivity of brain tissue to hypoxia, measurement of brain tissue oxygen ($PbtO_2$) has been implemented.

Although this measurement is exploited by catheters reporting local $PbtO_2$, some evidence suggests that PbtO2-based therapy combined with ICP/CPP-based therapy is associated with better outcome.

Nevertheless, the value of $PbtO_2$ as an independent prognostic variable has not yet been determined and indications about critical $PbtO_2$ values and how to manage them are still lacking [20].

Decompressive Craniectomy

Refractory raised ICP is defined as a situation when first-tier therapies to lower elevated ICP fail.

Decompressive craniectomy is performed with increasing frequency in this setting, since this intervention commonly reduces elevated ICP.

The prognostic value of such an invasive intervention is questionable. Available evidence suggests that in adults with severe diffuse traumatic brain injury and refractory intracranial hypertension, early bifronto-temporo-parietal decompressive craniectomy decreases ICP and the length of stay in the ICU but is associated with poorer outcomes [21].

Nevertheless, decompressive craniectomy is sometimes a last-resort, life-saving procedure and it is a very difficult decision not to undertake (see Chap. 1).

As patients submitted to decompressive craniectomy stabilize, cranioplasty is performed to restore the missing cranial vault. This typically occurs weeks or months after craniectomy.

This procedure has not only protective and aesthetic goals, but has some role in improving patients' clinical conditions.

Cerebral perfusion and cerebrospinal fluid dynamics are altered after decompressive craniectomy and the term "syndrome of the trephined" has been coined for the occurrence of delayed neurological, cognitive, and psychological symptoms following such an intervention. These symptoms may improve significantly after cranioplasty, which should not be delayed as soon as it is considered safe [22].

4.1.5.2 Mild TBI Prognosis

Although up to 95 % of TBIs are mild, studies addressing prognosis of mild TBI reported conflicting results.

Although the vast majority of mild TBI patients exhibit normal brain CT scan, several studies pointed out that the evidence of an abnormal CT scan after mild TBI is associated with a worse outcome.

Other studies suggested some univariate predictors of poor outcome, such as GCS, initial complaints (headache, nausea, and dizziness), and age. Posttraumatic amnesia (PTA) received much attention, since evidence exists that 80 % of cases with PTA <2 weeks exhibited a good recovery, while PTA >12 weeks is a perfect predictor of poor outcome [23].

A multivariate prognostic model has been developed specifically for mild TBI [24] and suggests that poor outcome is predicted by only two variables:

1. Age
2. Presence of extracranial injuries

The evidence of alcohol intoxication upon injury seems to exert a protective role, but this is conceivably purported by an overestimation of TBI severity in intoxicated patients.

The only neuroradiological characteristic that adds marginally to the prediction of outcome is the number of intraparenchymal hemorrhagic contusions.

Nevertheless, the whole model is a weak predictor of outcome after mild TBI.

With respect to moderate/severe TBI, it is quite evident how mild TBI is a qualitatively different nosocomial entity.

Quality of life after mild TBI seems to be affected by a number of occurrences that are not predictive of outcome after moderate/severe TBI, such as preexisting physical comorbidities, severe postconcussion symptoms, posttraumatic stress disorder, number of years of formal education, presence of nausea or vomiting on admission, and the pain levels seen early after injury.

It is noteworthy that hypotension/hypoxia, strong predictors of poor outcome after moderate/severe TBI, do not exert any role in outcome prediction after mild TBI. This suggests that the concept of secondary brain damage cannot be applied to mild TBI.

Trivial TBI may cause chronic subdural hematomas in the elderly. In this situation, corticodural vein disruption, more common in atrophic and poorly compliant aging brains, produces subdural hematomas over time (days or even months). The cognitive impairment associated with this syndrome variably regresses after surgical evacuation.

4.1.5.3 Posttraumatic Neurological Syndromes

Epilepsy

Seizures occurring after TBI are defined "early" if occurring within 7 days after trauma and "late" if occurring thereafter.

Early seizures are associated with the occurrence of adverse events (increase in ICP, hypertension, dysventilation, etc.) and increase the brain metabolic rate for oxygen, thus increasing the burden of secondary brain damage. Moreover, they can go unnoticed and status epilepticus may ensue with relevant brain damage. In fact, up to 22 % of ICU patients may exhibit seizures, 52 % of which are nonconvulsive, and the incidence of this phenomenon is heavily dependent upon the rate of EEG monitoring in the ICU.

Late seizures actually represent an outcome.

There is no evidence that antiepileptic prophylaxis may help in preventing late seizures and antiepileptic drugs themselves have well known adverse effects.

Some risk factors for late seizures have been indicated:

- GCS score <10
- Cortical contusion
- Depressed skull fracture
- Subdural hematoma
- Epidural hematoma
- Intracerebral hematoma
- Penetrating head wound
- Seizure within 24 h of injury

Dementia

A single TBI is a risk factor for Alzheimer's disease: 20–30 % of Alzheimer's patients suffered a mild to severe TBI at some point in their life.

Repeated mild TBI are even worse when long-term cognitive prognosis is considered, as reflected by the old-fashioned term "dementia pugilistica," now better known as "chronic traumatic encephalopathy," which specifically indicates dementia ensuing after repeated mild TBI.

The number of TBIs suffered throughout life is a major determinant of dementia, which is by no means restricted to boxers, but is characteristic of every activity in which recurrent TBI occurs. Female gender and APOE ε4 allele are also predisposing factors.

Amyotrophic Lateral Sclerosis

A history of TBI is positively associated with the occurrence of amyotrophic lateral sclerosis (ALS), especially when accompanied by other ALS risk factors such as cigarette smoking, radiation, electric shocks, and some intoxications (heavy metals, pesticides, etc.) [25].

In particular, repeated TBIs, even if mild, are reported to increase the risk of ALS up to an odds ratio of 1.7.

The latter consideration indicates some similarities with posttraumatic dementia, at least from an epidemiological point of view. This similarity is possibly reinforced by some evidence that the histological pattern may differ from between post-TBI ALS and sporadic ALS, with post-TBI ALS actually being a particular form of "tauopathy" [25].

Prolonged Impairment of Consciousness

Twelve months after TBI, the state of consciousness is commonly considered stable.

The level of consciousness impairment and its evolution is discussed in Chap. 36 (Comas).

Other Neurological Disorders

Although sometimes depicted as "minor," a number of neurological disturbances affects patients after TBI. These disorders have been referred to as "postconcussive syndrome" and may last for years after trauma.

Headache, light-headedness, dizziness, sleep disorders, fatigue, sensorial alterations, and psychiatric disorders (sometimes ascribable to posttraumatic stress disorder) variably affect post-TBI patients. Organic causes do not account for these disorders in the vast majority of cases.

4.2 Traumatic Spinal Cord Injury

4.2.1 Terminology and Definitions

Traumatic spinal cord injury (SCI) is an alteration of spinal cord function caused by external mechanical forces acting on the vertebral canal.

These forces may penetrate the vertebral canal (penetrating SCI) or leave it intact (blunt SCI).

Damage can be produced by forces directly hitting the spinal cord or, more frequently, by forces causing displacement of the spinal canal, fracture, or hemorrhage. Compression and/or ischemia are the main determinants of spinal cord injury.

Secondary damage may occur after SCI in a similar way as after TBI (Sect. 4.1.1). This accounts for worsening deficits and is largely preventable (Sect. 4.5.1).

Spinal cord injury affects some 40 per million people each year, but great regional variability is evident.

Males represent around 80 % of SCI patients.

4.2.2 Clinical Features

Acute neurological deficit ensues distal to the level of injury immediately after SCI.

This deficit encompasses all of the three components – motor, sensitive, and autonomic – to various degrees according to the extent of the anatomical spinal damage.

In the hours and days following SCI, "spinal shock" ensues. The mechanism of this condition, characterized by anesthesia and flaccid paralysis, is still not completely understood. More caudal and more complete spinal damages tend to exhibit prolonged spinal shock.

Spasticity progressively replaces the spinal shock state.

Lesions above C4 invariably produce respiratory failure, but more caudal cervical lesions may also impair ventilation because of respiratory auxiliary muscles deficit or cough impairment.

4.2.3 Diagnostic Markers

- History
  - Mechanism of trauma
  - Patient conditions before SCI
- Clinical examination
  - Neurological
    - Thorough neurological spinal examination
    - ASIA Scale (Sect. 4.5.2.1)

  - General
    - Ventilation
    - Hemodynamics
- MR
- Electrophysiological monitoring (Sect. 4.5.2.3)

(Lack of ability to monitor spinal cord physiology in real time is a major drawback in dealing with SCI)

4.2.4 Top Differential Diagnosis

The traumatic event and its temporal correlation with typical posttraumatic lesions usually exclude any differential diagnosis.

Patients affected by cognitive or sensory-motor disease may undergo SCI with increased frequency. Differentiating previous and ongoing disease may be challenging.

4.2.5 Prognosis

When dealing with SCI prognosis, the level of injury is a fundamental issue.

The degree of recovery after the initial injury is usually considered an important clinical measure of outcome.

Nevertheless, quality of life depends tremendously upon the level of injury. A paraplegic patient and a tetraplegic patient may have exhibited similar degrees of improvement in their respective initial neurological deficits, but their quality of life will not be the same.

Several scales have been proposed to measure quality of life after SCI, e.g., the functional independence measure (FIM) [26].

Hence the relative "evolution of neurological deficit" must be put into perspective by taking into account the absolute degree of neurological impairment.

After SCI, the degree of recovery of neurological function is proportional to the preservation of the original tissue at the injury site.

Complete medullary transection precludes any recovery.

Incomplete medullary lesions are associated with clinical changes over time.

In such cases, neurological deficit is theoretically maximal immediately after SCI, because of acute dysregulation of axon conduction. Improvement is expected to begin in hours or weeks after SCI and to plateau in the following 6–12 months.

Nevertheless, worsening of the presenting conditions may occur as:

- An ascent of neurological deficit level
- An increase of the presenting neurological deficit

This worsening is an expression of "secondary damage" and is believed to be largely preventable.

With respect to this concept, prognostic variables may address either the chance of worsening deficit or the degree of recovery. Similarly, active research on SCI therapies is targeted either to preserve residual axons or to repair them.

4.2.5.1 Prognosis of Worsening Deficit

Compression

Spinal cord compression due to fracture, dislocation, or hemorrhage in the spinal canal are major determinants of prognosis. It prevents potential recovery and actually causes worsening of SCI deficit.

Neurosurgical indications and timing to release and prevent compression are frequently updated. The most recent international guidelines can be found in the *Neurosurgery* March 2013 Supplement, which is entirely dedicated to this issue [27].

Occult motion of injured spinal segments may precipitate spinal cord compression and proper immobilization of SCI patients is mandatory until thorough MR evaluation and neurosurgical workup clearly state to what extent patients can be mobilized. This issue also received much attention in the aforementioned guidelines [27].

Ischemia

Post-SCI spinal cord hypoperfusion due to local compression or systemic hypotension may lead to worsening of the initial spinal damage.

Although several methods have been investigated in the experimental setting, no method is currently validated to measure reliably spinal cord blood flow.

A recommendation to maintain mean arterial pressure (MAP) above 80 mmHg has been issued. This mimics similar recommendations issued for traumatic brain injury (Sect. 4.5.1.4) and seems reasonable, since tolerance to ischemia, metabolic request for oxygen, and autoregulation impairment after trauma are similar between brain tissue and spinal cord. Unfortunately, this recommendation is not founded on evidence and both its effectiveness and safety have been questioned [28].

4.2.5.2 Prognosis of Recovery

As with moderate/severe TBI prognosis, the classical univariate approach to outcome prediction in SCI is insufficient and multivariate logistic predictive models combining various predictors of outcome in a possibly nonlinear fashion are recommended (Sect. 4.5.1). Some interesting models have been proposed in this setting [29] although a comprehensive prognostic model has yet to enter into clinical use worldwide.

Clinical Evaluation

The traditional, complete neurological spinal examination is the cornerstone of the evaluation of SCI.

The standardized approach in the evaluation of SCI patients is found in the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), which is revised on a regular basis by the International Standard Committee of the American Spinal Injury Association (ASIA) [30].

By the correct implementation of the ISNCSCI, SCI patients are classified according to the ASIA score for the severity of SCI, better known as ASIA Impairment Scale (AIS) (Table 4.6) [31].

The resulting AIS score has been recognized as an important predictor of outcome after SCI.

SCI classified as AIS-A have a very low chance of improvement.

Table 4.6 American Spinal Injury Association (ASIA) Impairment Scale (AIS)

Grade	Impairment	Description
A	Complete	No sensory or motor function is preserved in the sacral segments S4–S5
B	Sensory incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4–S5, *and* no motor function is preserved more than three levels below the motor level on either side of the body
C	Motor incomplete	Motor function is preserved below the neurological level, and more than half of key muscle functions below the single neurological level of injury have a muscle grade less than 3 (Grades 0–2)
D	Motor incomplete	Motor function is preserved below the neurological level, and at least half (half or more) of key muscle functions below the level of injury have a muscle grade >3
E	Normal	Sensation and motor function is normal (or same as before SCI) in all segments

AIS-D patients usually improve substantially.

AIS-B and AIS-C patients benefit from neurological improvement in 60–80 % of cases, but the degree of such improvement is quite variable and presently unpredictable.

Several efforts to improve the predictivity of the AIS score are ongoing.

Relevant examples of major strategies to reach this goal are:

- Incorporating an autonomic dysfunction evaluation in the score.

  Autonomic dysfunction heavily affects quality of life after SCI and its quantification deserves the same attention as sensitive and motor deficits.
- Implementing modern ordinal logistic regression analysis that takes into account nonlinearity.

Neuroimaging

Although CT scan can evidence vertebral derangement, its accuracy in showing intravertebral and spinal cord abnormalities is low and its prognostic value is poor.

MR is the examination of choice and is a good prognostic tool [32]; a completely negative MR is associated with good recovery.

Intraspinal hemorrhage greater than 1 cm in length and medullary edema extending longitudinally for more than 3 cm are associated with poor probability of improvement.

Moreover, MR contributes indirectly in improving SCI prognosis, since it offers the best definition of medullary and radicular compression, ligament and disc injury, and displacement of the vertebral column [27].

Areas of active research include several neuroradiological techniques stemming from MR, since they appear to be promising prognostic tools: e.g., functional MR (fMR) shows the integrity of neurological pathways, and diffusion tensor imaging (DTI) allows good visualization of white matter.

Neurophysiology

The subjectivity of clinical assessment may be overcome by motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs). Moreover, these tools provide indications about the integrity of the spinal cord even in the presence of confounding factors such as head injury, orthopedic or peripheral nerve injury, preexisting diseases, and sedation or intoxication.

The presence of retained MEPs and SSEPs is associated with higher probability of some recovery, while their absence is an ominous sign. MEPs and SSEPs are mostly employed during spinal surgery to limit ensuing surgical damage, but are rarely studied in the acute phase of SCI.

As stated above (Sect. 4.5.2.1), autonomic dysfunction evaluation [33] may be an important adjunct to the assessment of SCI prognosis.

Biochemical Markers

As for TBI (Sect. 4.5.1.9) several serum and CSF biomarkers of SCI severity have been investigated.

None of them may be considered independently prognostic, but future studies could identify a panel of them that could help assess prognosis.

Genetics

There is evidence that the APOE ε4 allele, which is linked to Alzheimer's disease and is involved in TBI prognosis (Sect. 4.5.1.10), is associated with reduced neurological recovery after SCI [34].

4.2.5.3 Prognosis

During the first year after trauma, several complications may cause death in SCI patients, mostly pulmonary (31 %), circulatory (15 %), and septic (12 %). Mortality rate during the first year is enormously dependent upon the level of injury, associated lesions, and the expertise of the caretakers.

Beyond the first year after trauma, SCI patients still present a reduced life expectancy (around 60 % with respect to normal for tetraplegic patients), with similar causes and variability.

Tetraplegic patients with lesions above C4 may require various degrees of ventilatory support, ranging from assisted to controlled ventilation. The need for prolonged ventilatory support carries an increased risk of death in any kind of patient because of pulmonary barotrauma and high pulmonary infection rate. In SCI patients, prolonged and even permanent ventilatory support, besides being itself a severe outcome, increases the risk of death with a relative risk between 2.5 and 3.5.

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Coma

5

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Key Facts

- **Terminology and definitions**
  - **Consciousness**: awareness of self and the environment.
  - **Coma**: unarousable unresponsiveness with closed eyes lasting more than 1 h.
- **Clinical features**
  - Closed eyes and no appropriate response to vigorous stimulation.
    Level of consciousness assessment: Glasgow Coma Scale (GCS), Full Outline of Unresponsiveness (FOUR), ACDU and AVPU scales.
- **Diagnostic markers**
  - **Laboratory** – Blood and urine screening (metabolic brain dysfunction, poisoning).
    CSF – bleeding, inflammatory diseases, bacterial and fungal staining, anti-viral Ab, specific PCR, cultures).
  - **Imaging** – TC (bleeding, brain edema, space-occupying lesions), MRI (gray and white matter damage, space-occupying lesions), DTI-MRI (white matter damage), PET (glucose hypo-metabolism).
  - **Neurophysiology** – EEG (seizure, arousal), SSEP (outcome and response to treatment).
- **Top differential diagnoses**
  - **Causes of coma**: structural (space-occupying and traumatic lesions, hydrocephalus, stroke, hemorrhage) vs metabolic brain dysfunction.
  - **Coma-mimicking events**: locked-in syndrome, Guillain-Barré, status epilepticus, psychogenic unresponsiveness.
- **Prognosis**
- Variable with:
  - **Causes of coma**: traumatic, cerebrovascular, toxic, metabolic.
  - **Treatment**: resuscitation and etiological.
  - **Baseline characteristics**: age, comorbidities, cardiac arrest (CA), quality and timing.
  - **Clinical examination**: motor response, papillary and corneal reflexes, myoclonus.
  - **Neurophysiology**: SSEPs (bilateral absence of the cortical N20 response of the median nerve), EEG (seizures).
  - **Biomarkers**: BiNeuron-specific enolase (NSE), S-100B.

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Abbreviations

ABC, Airway and protect C-spine, Breathing and Circulation; ADC, Apparent diffusion coefficient; CA, Cardiac arrest; CPC, Cerebral Performance Category; CPP, Cerebral perfusion pressure; CPR, Cardiopulmonary resuscitation; DTI, Diffusion tensor imaging; FPR, False-positive rate; ESE, Status epilepticus; FOUR, Full Outline of Unresponsiveness; GCS, Glasgow Coma Scale; ICP, Intracranial pressure; MCS, Minimally conscious state: NSE, Neuron-specific enolase; SB, Suppression burst

5.1 Terminology and Definitions

5.1.1 Consciousness

A state of full awareness of the self and full relation with the environment.

Consciousness requires both arousal activity and some degree of content (cognitive and affective activities). It may be impaired to various extents, so that the term "level of consciousness" is applied.

5.1.2 Acute Impairment of Consciousness

Several terms have been used to indicate the different states of impairment of consciousness and sometimes improper use or loose definitions arise from the popular use of them [1].

The most relevant to contemporary clinical practice are the following:

- Coma. Unarousable unresponsiveness with closed eyes lasting more than 1 h. It is the most severe impairment of consciousness, but it is usually a transitional state. In fact, after 1 month comatose patients either recover wakefulness and awareness or develop chronic disorders of consciousness (see below).
- Stupor. A "stunning" similar to coma, but the patient can be transiently aroused with vigorous stimulation.
- Obtundation. Reduction of the alertness with reduced interest in the environment.

5.1.3 Chronic Impairment of Consciousness [2]

These conditions may be primitive or, more often, occur after an acute impairment of consciousness (typically coma).

- Brain death. Irreversible loss of all functions of the brain. Due to its medico-legal implications, operative definitions of how to diagnose brain death are available. These definitions vary in different countries.
- Vegetative state. Cycling arousal with open eyes occurs, not associated with any cognitive activity. It may be a transitional state. Vegetative state is defined "persistent" if lasting more than 1 month. Further prolonging vegetative states are defined "permanent" if they exceed 3 months after resuscitated cardiac arrest, or 1 year after traumatic brain injury. "Coma vigil" and "apallic state" are obsolete terms to indicate the vegetative state.
- Minimally conscious state. Consciousness is severely impaired, but there is minimal, intermittent, and unsustained awareness of self and environment. It may be a transitional state, too.
- Akinetic mutism. Sleep-wake cycles are present without evidence of mental and spontaneous motor activity.

5.2 Clinical Features

Coma states can be classified in two main categories according to etiology:

- Coma from structural causes. Lesions diffusively affecting both cerebral hemispheres or directly affecting the ascending reticular activating system cause impairment of conscious level (e.g., traumatic brain injury and hemorrhagic or ischemic stroke).
- Coma from metabolic causes. Consciousness is impaired by toxic agents, either endogenous (e.g., hepatic coma, diabetic coma) or exogenous (e.g., barbiturate coma, severe organophosphate poisoning).

Coma and impaired consciousness are common presentations in the neurocritical patient. Impaired consciousness is a sign of impending irreversible damage.

Comatose patients usually lie with closed eyes and cannot respond appropriately even to vigorous stimulation. Accurate and reiterated evaluation of the level of consciousness is mandatory. In order to provide a standard for this purpose, several different scales are used to evaluate the level of consciousness. The ACDU and AVPU (see Chap. 4) are simple, accurate, and easy to use [3]. The Glasgow Coma Scale (GCS) (see Chap. 4) is widely employed and it is probably the best scale for trauma patients [4] (for a more extended discussion of the GCS see Chap. 4). The Full Outline of Unresponsiveness (FOUR) (see Table 5.1) provides more neurological detail than the GCS [5].

An U score on ACDU, a P score on AVPU, or a GCS score ≤8 indicates coma.

Table 5.1 Full Outline of Unresponsiveness

Eye response	0	Eyelids remain closed with pain
	1	Eyelids closed but open to pain
	2	Eyelids closed but open to loud voice
	3	Eyelids open but not tracking
	4	Eyelids open or opened, tracking or blinking to command
Motor response	0	No response to pain or generalized myoclonus status
	1	Extension response to pain
	2	Flexion response to pain
	3	Localizing to pain
	4	Thumbs up, fist or peace sign
Brainstem reflex	0	Absent pupil, corneal and cough reflex
	1	Pupil and corneal reflexes absent
	2	Pupil or corneal reflexes absent
	3	One pupil wide and fixed
	4	Pupil and corneal reflexes present
Respiration	0	Breathes at ventilator rate or apnea
	1	Breathes above ventilator rate
	2	Not intubated, irregular breathing
	3	Not intubated, Cheyne-Stokes breathing pattern
	4	Not intubated, regular breathing pattern

Total score is the sum points for all four parameters. Minimum score = 0, maximum score = 16. the lower the score, the deeper the coma

5.3 Diagnostic Markers

History regarding the circumstances of coma occurrence should be obtained from bystanders.

Similarly, the patient's previous clinical history should be obtained.

The basic neurological examination provided by the aforementioned coma scales should be extended to better evaluate cranial nerve function, somatic motor and sensory function, and respiration patterns.

General clinical examination and appropriate blood and urine analyses are mandatory to rule out some causes of coma and to provide baseline assessment of patients.

Noncontrast computed tomography (CT) – Is the examination of choice to detect structural

lesions and intracerebral bleeding. CT angiography: intracerebral vessel stenosis. Perfusion CT: cerebral areas of hypoperfusion.

MR – Is not always readily available, is time-consuming; should be reserved to hemodynamically stable patients.

Cerebral angiography – To determine the source of subarachnoid hemorrhages or thrombosis.

Lumbar puncture: meningitis or subarachnoid hemorrhage. Should be performed after CT scan to avoid its ominous side effects.

Electroencephalogram (EEG) for seizures (see Chap. 4). Its routine use in comatose patients in the ICU has been advocated to rule out subclinical status epilepticus.

5.4 Differential Diagnosis

The diagnostic tools described in the previous paragraph are essential in the work-up of the differential diagnosis of the causes of coma. Appropriate treatment of the underlying causes is mandatory to improve the prognosis of comatose patients.

Another differential diagnosis challenge may be the differentiation of coma from another state mimicking it, such as the following:

- The locked-in syndrome. Locked-in patients are de-efferented and tetraplegic; not unconscious. Vertical eye movements and eyelid opening are preserved. EEG reactive alpha rhythm is preserved (alpha coma).
- Guillain-Barré syndrome. In rare cases, it can lead to complete de-efferentation.
- Status epilepticus and post-critical state.
- Psychiatric states. Some severe psychiatric conditions may mimic coma.

5.5 Prognosis

No comprehensive multifactorial model for outcome prognosis in comatose patients is available. Basically, the prognosis of coma depends not only upon its severity and duration, but also upon its underlying etiology. Coma is not a disease, but the expression of an underlying pathology.

Coma produced by hypoxia-anoxia due to cardiac arrest (CA) is considered a paradigm for non-traumatic coma. Moreover, it should be kept in mind that CA may occur as a consequence of any event per se causing unconsciousness: in these cases, the prognostic burden is carried both by CA-related hypoxia-anoxia and by the original triggering event.

Neurological outcome after coma is usually measured with the Cerebral Performance Category scale (CPC – see Table 5.2) [6] or the Modified Ranking scale (see Table 5.3) [7]. For coma ensuing after traumatic brain injury, specific scales such as the Glasgow Outcome Scale and the extended Glasgow Outcome Scale have been devised (see Chap. 4).

The optimal time-point for gaining clinical and instrumental data to assess outcome after CA was previously set at 72 h after the event [8], since the specificity of several indicators of poor outcome reached 100 % at this time-point. Although this indication may still be valid for non-traumatic comas, the induction of therapeutic hypothermia [9, 10] suggests a later evaluation. In fact, sedation and neuromuscular blockade used during the cooling period reduced the turnover of drugs due to hypothermia. Moreover, the direct effect of hypothermia on the brain led to the recommendation that comatose patients should be evaluated not earlier than after 72 h in normothermia (often 4–5 days after CA) and after complete clearance of sedative and analgesic drugs [11].

5.5.1 Causes of Coma

Traumatic coma has a better prognosis than non-traumatic coma. Among non-traumatic states, coma due to cerebrovascular disease carries the worst prognosis, while toxic and metabolic etiologies tend to do somewhat

Table 5.2 Cerebral Performance Category (CPC)

1	Good cerebral performance: conscious, alert, able to work, might have mild neurological or psychological deficit	Good outcome
2	Moderate cerebral disability: conscious, alert, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment	
3	Severe cerebral disability: conscious, dependent on other for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis	Poor outcome
4	Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness	
5	Brain death	

CPC scores are used to classify neurological status among survivors of CA in good (CPC 1–2) or poor (CPC 3–5) outcome

Table 5.3 Modified Rankin Scale

0	No symptoms	Good outcome
1	No clinically significant disability despite symptoms. Able to carry out all usual duties and activities	
2	Slight disability. Unable to carry out all previous activities, but able to look after own affairs without assistance	
3	Moderate disability. Requiring some help, but able to walk without assistance	
4	Moderately severe disability. Unable to walk without assistance and unable to attend to own bodily needs without assistance	Poor outcome
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention	
6	Death	

The Modified Rankin Scale is used for measuring the degree of disability or dependence in daily activities and for detecting clinical outcome

better, with 25 % of patients exhibiting a good recovery.

Hypoxic coma is associated with the highest mortality rate among the different causes of coma (80–90 %). Approximately 80 % of patients with successful restoration of spontaneous circulation after cardiopulmonary resuscitation (CPR) remain in a comatose state [12] and approximately one third of these regain consciousness [13].

5.5.2 Therapy

Adequate treatment heavily influences outcome in coma states.

In order to warrant survival, unconscious patients should be approached with the ABC criterion of resuscitation before any diagnostic effort is made. This approach indicates that

- Airway protection
- Breathing
- Circulation

should be evaluated and treated if impaired according to a standard procedure [14, 15].

Further treatment of coma states is dictated by recognition and correction of its underlying causes (e.g., neurosurgical management of space-occupying lesions, correction of metabolic disorders, treatment of severe infection or of intoxication). Induced hypothermia decreases morbidity and mortality and improves neurological outcome after CA [9, 10].

Regardless of the etiology of coma, prolonged treatment of comatose patients heavily relies on correct intensive care management.

As long-term care is at stake, nursing and physiotherapy remain cornerstones of the appropriate treatment of unconscious patients.

5.5.3 Baseline Characteristics

Two patient characteristics, namely age and comorbidities, affect the outcome and its time-

line in comatose patients. Nevertheless, these variables have poor accuracy in discriminating patients with good and poor outcomes [8, 11].

In CA patients, several variables related to cardiopulmonary resuscitation affect the outcome, such as the time from CA to the beginning of cardiopulmonary resuscitation, the quality of cardiopulmonary resuscitation itself, and the occurrence of even short periods of return of spontaneous circulation. These variables are heavily interrelated and although a 3–5 min time without cardiac circulation is deemed ominous, it is hard to identify prognostic criteria based on CA characteristics.

5.5.4 Clinical Examination

Several clinical signs have been correlated with the severity of coma.

Three signs received particular attention as poor-outcome predictors [16]:

- The absence of any motor response to pain
- The bilateral absence of corneal reflex, with 4 % false-positive rate
- The bilateral absence of pupillary light reflex, with 1 % false-positive rate

Myoclonus appears as spontaneous, repetitive, unrelenting, generalized clonus involving the face, limb, and axial musculature and an EEG pattern characterized by possibly coexisting recurrent epileptiform activity and discontinuous suppression burst. Myoclonus suggests severe hypoxic injury and is considered an ominous sign, but it does not have any role as a prognostic factor in patients treated with hypothermia [10].

5.5.5 Neurophysiology

5.5.5.1 Somatosensory Evoked Potentials (SSEPs)

Bilateral absence of the cortical N20 response of the median nerve SSEP is a very reliable predictor of poor outcome, with a false-positive rate approaching 0 % [11, 16].

Maintenance of N20 identifies only a fraction of survivors. Additional patients with poor neurological outcome can be identified by means of the of middle and long latency cortical response analysis: absence or prolonged latency of the N20 peak (>130 ms) has always been associated with death or a vegetative state [17].

5.5.5.2 EEG

Both spot EEG and continuous EEG monitoring are recommended [18, 19].

Suppression burst EEG patterns and recurrent epileptic activity or status epilepticus are relatively common during coma (although their incidence is unknown). These patterns are also ominous signs during induced hypothermia, which can indeed conceal them just as sedatives or neuromuscular blockade do [11, 16].

Seizures may cause adjunctive cerebral damage and should be aggressively treated, but no studies have examined the efficacy of aggressive anticonvulsant medication in post-CA comatose patients [10].

5.5.6 Biomarkers

BiNeuron-specific enolase (NSE) is the neural form of the intracytoplasmic glycolytic enzyme enolase found in neurons. A neural injury can be detected by the presence of increased levels of NSE in the cerebrospinal fluid or blood. In normothermic patients, serum NSE level >33 μg/L between 24 and 72 h after CA accurately predicts poor outcome [10]. On the other hand, in hypothermic patients, serum NSE level >33 μg/L are inaccurate in predicting outcome and values >80 μg/L should be considered predictive of poor outcome [16]. Alternatively, hypothermic patients should have serum NSE tested after recovery of normothermia [11].

S-100B has been extensively studied for neurological prognostication, but its role has not been established [11].

5.5.7 Imaging

CT scan and MRI performed shortly after CA are not useful in predicting which patients will regain consciousness; serial CT scan or MRI can provide clues to prognosis by showing anatomical damages of the brain [2].

Evidence of brain edema during the first few days of coma have poor predictive value [10].

MRI is more sensitive in detecting anoxic brain injury and quantifying its degree. Widespread diffusion-weighted abnormalities with DWI sequences or apparent diffusion coefficient (ADC) depression correlate with poor outcome [10]. Diffusion tensor imaging (DTI) reveals extensive white matter damage in patients with anoxic brain injury after CA. For this reason, DTI seems to be a promising tool to predict unfavorable outcome in comatose survivors of CA [12]. Moreover, functional MRI can demonstrate brain activity similar to that of normal control subjects following auditory and tactile stimulation as an index of good outcome [2].

However, MRI has not yet been validated as a predictive tool in comatose patients [10].

Global cerebral glucose metabolism measured by PET scan is not useful as a prognostic tool during coma. Indeed, it is reduced by ≥50 % in the majority of comatose patients and in patients with chronic disorder of consciousness. Nevertheless, the activation of primary and secondary cortical areas due to auditory and visual stimulation during PET scanning is a favorable sign, since it suggests that some of the neural networks necessary for consciousness are intact [2].

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Sleep Disorders

6

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Abbreviations

AD, Alzheimer's disease; AHI, Apnea-hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure; CSA, central sleep apnea; CT, computed tomography; EDS, Excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; LBD, Lewy body dementia; MAD, maxillary advancement device; MSLT, Multiple Sleep Latency Test; MR, magnetic resonance imaging; NFLE, nocturnal frontal lobe epilepsy; NIH, *National Institutes of Health;* NREM, non REM; OSAS, obstructive sleep apnea syndrome; PD, Parkinson disease; PLM, periodic leg movements during sleep; PSG, polysomnography; RBD, REM behavior disorder; REM, rapid eye movement; RLS, Restless leg syndrome; SOREMP, sleep onset REM period; SWS, slow-wave sleep; UARS, Upper airways resistance syndrome.

6.1 Introduction

The most relevant sleep disorders for the neurologist are (1) sleep-related breathing disorders, (2) parasomnias, (3) insomnias, (4) hypersomnias, and (5) restless leg syndrome.

6.2 Sleep-Related Breathing Disorders

Sleep-related breathing disorders include a variety of disorders, the most common and most relevant in the clinical practice being obstructive

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sleep apnea syndrome (OSAS). This condition is caused by a mechanical obstruction of the upper airways during sleep. Central sleep apnea (CSA), due to a loss of sensitivity of the chemoreceptors and neural activity in the brainstem, is another important disorder [1].

Key Facts

- **Definitions and terminology** – OSAS: repetitive episodes of mechanical upper airway obstruction that occur during sleep.
  - **OSAS severity**: based on polysomnographic AHI (apnea-hypopnea index). Mild: AHI 5–15; moderate: AHI 16–30; severe: AHI >30.
- **Clinical features** – Snoring apneic episodes; excessive daytime sleepiness (EDS); unrestorative sleep; nocturia.
- **Diagnostic markers**
  - **Imaging (CT/MR)** – Abnormalities of the upper airways and/or mandibular-pharyngeal.
  - **Neurophysiology** – Sleep hypopneas-apneas and sleep fragmentation (EEG arousals) at nocturnal polysomnography.
- **Top differential diagnoses**
  - Central sleep apnea syndrome, primary snoring, upper airways resistance syndrome (UARS), periodic limb movement disorder, narcolepsy, idiopathic hypersomnia, insufficient sleep syndrome.
- **Principles of treatment**
  - Diet, continuous positive airways pressure (CPAP), mandibular advancement devices (MAD), nasal, palato-pharingeal, and maxillo-facial surgery. OSAS is an independent risk for cardiovascular diseases and stroke in adults, and for behavioral disturbance in children.
- **Prognosis** –Risk factor of hypertension, cardiovacular diseases, methabolic dysregulation and stroke.

6.2.1 Definition

Obstructive sleep apnea syndrome (OSAS) (also known as sleep apnea, obstructive apnea, upper airway apnea, hypersomnia sleep apnea syndrome) is a sleep breathing disorder characterized by repetitive episodes of upper airway obstruction that occur during sleep. OSAS is graded on a scale based on the apnea-hypopnea index (AHI). It is defined by the mean number of apneas and hypopneas per hour of sleep. An AHI of 5–15 is considered a mild disturbance, 16–30 is considered moderate, and >30 is considered severe.

6.2.2 Clinical Features and Epidemiology

OSAS prevalence is variable depending on sex and age: male 4 %, female 2 %, children 2 %. Childhood form: from 0 to 10. Adult form: from 40 to 60 (women are more likely to develop OSAS after menopause).

A long history of snoring generally precedes the onset of OSAS, with snoring a most typical OSAS symptom.

Bed-partners may also report apneic episodes, often associated with arousal to restart breathing (choking or suffocation may be reported). Excessive daytime sleepiness (EDS) is the most typical presenting complaint. Driving accidents are frequently related to EDS.

Patients typically feel unrestored by nocturnal sleep, and may describe mouth dryness upon awakening and/or morning headaches that may last from one to several hours.

Nocturia (1–5 times per night) is frequently reported and it is related to the severity of the syndrome. Gastroesophageal reflux can occur in association with the effort to re-establish breathing. Secondary symptoms include psychiatric disturbances such as mood disorder, anxiety, and irritability. A loss of libido and erectile ability may also be reported.

Cardiac arrhythmias may occur during sleep in patients with OSAS; and hypertension with an elevated diastolic pressure values is commonly observed.

6.2.3 Diagnostic Markers

Blood, CSF, Genetics: n.s.

Imaging Cephalometric radiographs, magnetic resonance imaging (MR), computed tomography (CT) scanning, fiberoptic endoscopy, and drug-induced sleep endoscopy can all show abnormal anatomy or obstruction of the upper airways and/or mandibular-pharyngeal abnormalities. In childhood, tonsillar and/or adenoids enlargement is typically observed.

Neurophysiology The gold standard for OSAS diagnosis is the all-night polysomnography (PSG). In adult patients PSG must document >5 obstructive apneas/hypopneas of more than of 10 s per hour of sleep, associated with significant arterial oxygen desaturation. EEG arousals related to apneas/hypopneas and bradytachycardia runs are part of the typical polysomnographic presentation.

The Multiple Sleep Latency Test (MSLT) may be used to objectively measure EDS. The Epworth Sleepiness Scale (ESS) is routinely used to assess subjective sleepiness.

6.2.4 Differential Diagnoses

Common differential diagnoses include narcolepsy, idiopathic hypersomnia, insufficient sleep syndrome, and periodic limb movement disorder.

Other sleep breathing disorders (central alveolar hypoventilation, central sleep apnea syndrome, Cheyne-Stokes respiration, primary snoring. Upper airways resistance syndrome (UARS), paroxysmal nocturnal dyspnea) can be differentiated by OSAS by performing a PSG study.

Panic attacks, sleep choking syndrome, and sleep-related laryngospasm can occasionally be misdiagnosed as OSAS. Sleep-related gastroesophageal reflux and sleep-related abnormal swallowing syndrome can also produce choking episodes.

6.2.5 Principles of Treatment

Obesity is a major risk factor for OSAS. Reduction of excessive weight is an important therapeutic goal in almost all OSAS patients. Continuous positive airway pressure (CPAP) is the recommended treatment for sleep apnea.

Generally, severely symptomatic patients (severe EDS with AHI >30 events/h) readily improve with CPAP therapy. Conversely, in asymptomatic patients (no or mild EDS present), even with a markedly elevated apnea/hypopnea index, the clinical therapeutic CPAP effect may be difficult to appreciate by the patient. In mild OSAS, oral appliances (mandibular advancement devices) can be considered as a valid alternative to CPAP.

Various techniques of soft tissue surgery for treatment of OSAS have been proposed but their efficacy still remains controversial. An exception is adeno-tonsillectomy: it is almost always successful in children, but also in adult patients with well-documented tonsillar hypertrophy.

Facial-maxillary surgery can be very effective in selected patients.

6.2.6 Prognosis

OSAS in adult patients is a well-recognized independent risk factor and National Institutes of Health (NIH) guidelines include OSAS as an identifiable cause of hypertension. An apnea-hypopnea index of 15 events/h or more was independently associated with a threefold increased risk of developing hypertension.

Cardiovascular diseases associated with OSA include heart failure, stroke, cardiac arrhythmias, myocardial ischemia, and pulmonary arterial hypertension [2–4].

In addition, OSAS may be associated with metabolic dysregulation (insulin resistance and lipid disorders), which in turn is a risk factor for cardiovascular diseases.

Strong evidence indicates that OSAS is an independent risk factor for stroke [2]. Moreover,

OSAS exacerbates damage produced by a stroke and increases the risk for a subsequent stroke.

In children, the most relevant long-term consequences of OSAS are behavioral and neurocognitive morbidities. Behavioral dysregulation is commonly considered as a comorbidity of OSAS, but several authors report some association between OSAS and hyperactivity, attention deficits, impulsivity, and attention deficit hyperactivity disorder-like symptoms. Last but not least, EDS related to OSAS is a risk factor for motor vehicle accidents (estimated OR = 6.3) [5].

6.3 Parasomnias

Parasomnias are undesirable motor and behavioral phenomena occurring during sleep, at sleep-onset, or during sleep-arousals [1]. The type and complexity of movements and behaviors observed can vary according to the sleep stage (NREM or REM) and to the form of parasomnia. The patient is usually unaware of the parasomnic episode, which can be characterized by finalistic actions. The subject may awake during or at the end of the paroxysmal episode; a dreamlike memory can sometimes be reported after awakening, above all in REM parasomnias.

Key Facts

- **Definitions and terminology** – NREM parasomnias: undesirable physical, behavioral, or experiential events occurring during NREM sleep; NREM parasomnias are subclassified in several different disorders including confusional arousal, somnambulism or sleep-walking, sleep terrors or pavor nocturnus.
- **Diagnostic markers**
  - **Neurophysiology** – Diffuse hypersynchronous high voltage EEG delta activity during episodes; episodes occurring during slow-wave NREM sleep.
- **Top differential diagnoses**
  - Sleep-related epilepsy, nocturnal frontal lobe epilepsy, REM parasomnias (REM behavior disorder), nocturnal psychogenic nonepileptic seizures, nocturnal panic attacks, sudden awakenings in OSAS.
- **Principles of treatment and prognosis**
  - Treatment not necessary in sporadic episodes; 5-OH-tryptophane, clonazepam, antiepileptic drugs (severe cases). NREM arousal disorders usually have onset during childhood and a spontaneous disappearance within adolescence. Occasionally, they persist later on, during adolescence and adulthood.

6.3.1 NREM Parasomnias

6.3.1.1 Definition

NREM parasomnias (arousal disorders, somnambulism) [common definition] are undesirable physical, behavioral, or experiential events occurring during NREM sleep.

6.3.1.2 Clinical Features and Demographics

The prevalence of NREM parasomnias or NREM arousal disorders in the general population is around 1–6 % without significant gender differences [6, 7].

Age: prevailing in childhood, possible persistence, or onset in adolescence and adulthood.

6.3.1.3 Clinical Presentation

NREM arousal disorders occur during slow-wave sleep (SWS) and are divided into three forms: confusional arousals, sleep-walking (somnambulism), and sleep terrors (pavor nocturnus). The clinical manifestations of the three main types of arousal parasomnias can coexist in the same individual and sometimes also in the same episode. Episodes are typically sporadic, occurring during the initial third or first half of the night. Some authors have emphasized the frequent comorbidity between nocturnal

frontal lobe epilepsy (NFLE) and arousal disorders [7, 8]. In some groups of NFLE patients, the prevalence of parasomnias can reach percentages (34 %) much higher than the prevalence of arousal disorders in the general population (1–6 %). It could be hypothesized that these two disorders, even if etiologically different, could share a common pathophysiological mechanism, acting through an alteration of the arousal regulatory system.

6.3.1.4 Diagnosis

Genetics A family history of NREM parasomnias is a major risk factor. Specific genetic alterations have not been identified yet.

Imaging (CT/MR) – ns

SPECT Scan Regional activation during episodes (i.e., hyperperfusion) of cingulate and motor areas, with frontal deactivation has been described [9].

Neurophysiology
Video-polysomnography is the gold standard for the diagnosis of NREM parasomnias [10]. During the episodes, the EEG is characterized by a diffuse hypersynchronous high voltage delta activity typical of the SWS. Episodes occur during slow-wave NREM sleep.

6.3.1.5 Differential Diagnoses

Sleep-related movement disorders (usually characterized by simple, non-goal-directed, and non-dream-related movements). Sleep-related epilepsies [10, 11]. Nocturnal psychogenic non-epileptic seizures and/or nocturnal panic attacks.

6.3.1.6 Principles of Treatment

Treatment is not usually necessary if episodes are sporadic. When necessary, benzodiazepine (first choice: clonazepam 0.5-2 mg at night), 5-OH-tryptophane, antiepileptic drugs (i.e., carbamazepine, topiramate) can be used in selected cases.

6.3.1.7 Prognosis

NREM arousal disorders usually show onset during childhood and then a spontaneous disappearance within adolescence. Occasionally, they persist later on, during adolescence and adulthood. When episodes are frequent and especially if they are drug resistant, sleep disruption and social disability can occur. In severe cases, injuries (to the patient or to the bed-partner) may be a consequence of violent, nocturnal behaviors.

6.3.2 REM Sleep Behavior Disorder (RBD)

6.3.2.1 Terminology and Definitions

Synonyms Oneirism, idiopathic RBD, symptomatic RBD, REM sleep without atonia, REM sleep motor Parasomnia

6.3.2.2 Definition and Clinical Features

RBD is characterized by the intermittent loss of REM sleep atonia and by the appearance of elaborate motor activity associated with dream mentation. The dreams often involve kicking, screaming, punching, grabbing, and even jumping out of bed. When awoken, the patient may recall the dream matching the actions he was performing [1].

RBD episodes typically occur in the second part of the night. RBD patients show motor and verbal activity, consistent with dream content that can be remembered after awakening. Movements of the limbs and/or of the head and the trunk are typically rapid and short lasting, verbalization can be easily understandable. The non-complete loss of physiological REM muscle atonia does not allow the patients to walk and they sometimes fall on the ground with traumatic injuries. Anosmia can be present in the early phase of the disease [12].

Prevalence From 1 to 5 % in general population. The prevalence increases up to 30 % among patients affected by synucleinopathies (Parkinson's disease, dementia with Lewy bodies), reaching the prevalence of up to 90 % among patients with multiple system atrophy [6]. RBD is much more frequent in male than in female patients

Onset: after 50 years (mean 60 years, range 36–84 years); persistence in senescence.

6.3.2.3 Diagnostic Markers

Blood, CSF – ns

Genetics – A family history of REM parasomnias is a major risk factor. Specific genetic alterations have not been identified.

TC; MR: ns. Brain atrophy in RBD associated with neurodegenerative disorders.

Neurophysiology

Video-PSG: loss or reduction of physiological muscular REM atonia on EMG channels.

EEG: sleep structure could show a fragmentation and the occurrence of numerous short arousals, above all during REM sleep.

6.3.2.4 Pathology

Depending on the associated underlying diseases (synucleinopathies and other neurodegenerative disorders). Neuronal loss and Lewy pathology (α-synuclein-containing Lewy bodies) were found in the brainstem nuclei that regulate REM sleep atonia [13, 14].

6.3.2.5 Top Differential Diagnoses

Sleep-related epilepsy, nocturnal frontal lobe epilepsy, NREM arousal disorders, nocturnal psychogenic nonepileptic seizures or nocturnal panic attacks, sleep-related movement disorders.

6.3.2.6 Principles of Treatment

Treatment is not usually necessary if episodes are sporadic. When necessary, clonazepam 0.5–2 mg at night and/or melatonin and/or antiepileptic drugs in most severe cases. Protective measures can be used to avoid injuries.

6.3.2.7 Prognosis

RBD is usually a chronic disorder, with onset during adulthood at around 50 years and persistence through senescence. It is not usually a disabling disorder if episodes are sporadic; when they are frequent and/or drug-resistant, sleep disruption, social disability, and possible risk of traumatic injuries can occur.

Up to 80 % of individuals diagnosed with idiopathic RBD can develop a Lewy body disorder with time (10–15 years on average after RBD onset). The great majority of patients who developed a neurodegenerative disease showed Parkinson's disease or a Lewy body dementia (LBD) or a multiple system atrophy. Alzheimer's disease (AD), sometimes combined with LBD, and progressive supranuclear palsy are less frequently observed. Hence,

Key Facts

- **Terminology and definitions** – REM parasomnias are undesirable physical, behavioral, or experiential events occurring during REM sleep. REM parasomnia are subclassified in several different disorders including REM behavior disorder (RBD), recurrent isolated sleep paralysis, nightmare disorder.
- **Clinical features** – Motor and behavioral phenomena during REM sleep.
- **Diagnostic markers**
  - **Blood, CSF, Genetics, Imaging (CT/MR)** – ns.
  - **Neurophysiology** – Video-PSG: loss or reduction of physiological muscular atonia on EMG channels during REM sleep.
- **Top differential diagnoses** – Sleep-related epilepsy, nocturnal frontal lobe epilepsy, NREM parasomnias, nocturnal psychogenic non epileptic seizures, nocturnal panic attacks, sleep-related movement disorders, sudden awakenings related to OSAS.
- **Principles of treatment and prognosis** – Low-dose clonazepam, melatonin, antiepileptic drugs (severe cases).
  - RBD is a chronic disorder, with onset during adulthood at around 50 years and persisting through senescence.

RBD can characterize the prodromal phase of a Lewy body disorder. Olfactory system degeneration represents one of the first events in brainstem nuclei progressive degeneration, causing anosmia in a preclinical stage both of RBD and of PD [14, 15].

6.4 Insomnia

Key Facts

- **Terminology and definitions** – Insomnia (primary or secondary): repeated difficulties in sleep initiation, duration, consolidation, or quality resulting in some form of daytime impairment. Insomnia is defined chronic for duration >1 month.
- **Clinical features** – Difficulty in falling asleep; sleep fragmentation; hypnotic and/or alcohol abuse; exhausting sleep; daytime drowsiness or fatigue; mood disorders.
- **Diagnostic markers**
  - **Blood, CSF, Imaging and Genetics**: ns
  - **Video-PSG**: spontaneous sleep fragmentation; PLM and OSAS should be excluded.
- **Top differential diagnoses** – Restless leg syndrome (RLS), periodic leg movements during sleep (PLM), sleep-disordered breathing (including OSAS), psychiatric disorders, substance/drug abuse, circadian sleep disorders.
- **Treatment and prognosis** – Benzodiazepine-receptor agonists (Z hypnotics), benzodiazepines, melatonin (circadian rhythm disorders), sedative antidepressant, sedative antipsychotics (selected cases), psychological treatments (cognitive behavioral therapy). Psychophysiological insomnia may persist for decades and may gradually worsen.

6.4.1 Definition and Clinical Features

Insomnia is defined as repeated difficulties in sleep initiation, duration, consolidation, or quality, occurring despite adequate time and opportunity for sleep and resulting in some form of daytime impairment. In children, the sleep difficulty may consist of observed bedtime resistance or inability to sleep independently.

Demographics Episodic insomnia incidence is 30–50 %. Chronic insomnia: 10–15 % (M:F = 1.5:1). Incidence increases with age (except for idiopathic insomnia which appears early in childhood).

Clinical Features Insomnia onset may be insidious or acute. In the acute form often a stress factor may be identifiable as an initial trigger. Daytime symptoms include fatigue, decreased mood/irritability, general malaise, and cognitive impairment, proneness for errors/accidents at work or while driving, tension headaches, and concerns or worries about sleep.

Insomnia may also relate to primary medical illnesses, mental disorders, other sleep disorders, and substance abuse. In such cases, it is defined as secondary Insomnia.

Insomnia should be subdivided in several different subtypes including the following:

- Psychophysiological insomnia, paradoxical insomnia (formerly sleep state misperception), adjustment sleep disorder (acute insomnia), inadequate sleep hygiene, idiopathic insomnia
- Behavioral insomnia of childhood
  - Limit-setting sleep disorder
  - Sleep-onset association disorder
- Other insomnia associated with a known physiological/medical condition
- Other insomnia due to a substance abuse

The analytical description of all these forms of insomnia is outside the aim of the present volume. We will describe the general characteristics of insomnia with particular reference to insomnia complaints in patients affected by neurological disorders.

6.4.2 Differential Diagnosis

Restless leg syndrome (RLS), periodic leg movements during sleep (PLM), sleep fragmentation due to sleep-disordered breathing, psychiatric disorders (depression, anxiety, bipolar disorders, mania, etc.), substance/drug abuse, circadian sleep disorders.

Insomnia in Neurological Disorders

Insomnia and/or sleep fragmentation characterize several neurodegenerative diseases such as synucleopathies (Parkinson's disease, dementia with Levy bodies, multiple system atrophy) and tauopathies (AD disease, fronto-temporal dementia, progressive supranuclear palsy) [18–21]. Insomnia has also been associated with various inflammatory pathologies of the CNS, with neuromuscular disorders and ischemic or traumatic brain pathologies. The prevalence of insomnia in neurological disorders is estimated to be between 30 and 100 %, depending on the disease. Insomnia can be a direct consequence of the underlying disease or represent a secondary manifestation of other factors associated with the underlying condition such as depression, pain, or side effects of drug therapies.

Almost all patients with Parkinson disease (PD) complain of sleep disorders and its prevalence is estimated between 60 and 90 %.

Insomnia with sleep fragmentation is the most substantial disorder in PD, with a significant increase in the frequency of awakenings and sleep latency. Patients with PD may report difficulty falling asleep, but more frequently complain of frequent and prolonged awakening during the night. Psychiatric and psychological factors may also contribute to sleep dysregulation. Frequently in PD, insomnia can be a symptom related to concomitant RLS.

The presence of sleep disorders such as hypersomnolence, sleep fragmentation, and early awakening are present in about one third of patients with Alzheimer's disease.

6.4.3 Principles of Treatment

Psychological and behavioral interventions are indispensable and effective for most insomnia sufferers.

Benzodiazepine and benzodiazepine-receptor agonists, such as zopiclone and zolpidem, are used for acute forms. Sedating antidepressants (e.g., doxepin, amitriptyline, mirtazapine, trimipramine, trazodone) and sedating antipsychotics (e.g., quetiapine, olanzapine) should be preferred in chronic insomnia. Melatonin use in insomnia is still debated.

6.4.4 Prognosis

Psychophysiological insomnia may persist for decades and may gradually worsen as a vicious cycle of fitful sleep, daytime irritability, and poor concentration. Complications of persistent insomnia include a significantly higher risk for first occurrence or recurrence of major depression and excessive use of prescription or over-the-counter sleep aids. A sense of repeated failure to resolve sleep problems often leads to intermittent periods of resigned helplessness and help-seeking behaviors.

Experimental partial sleep deprivation studies in humans demonstrated that a sleep time reduced below 7 h per night has consequences on cognition [16]. Patients who suffer from insomnia subjectively complain of a reduction in work performances, cognitive, memory, and attention deficits.

Studies of the cognitive effects of insomnia have some intrinsic limitations due to the heterogeneity of the clinical picture; however, a negative impact of insomnia both on procedural and declarative memory has been reported. Increase in the latency of responses and extreme variability in reaction times compared to controls with normal sleep patterns have been described. In elderly patients with insomnia, a reduction in the

ability to maintain focused attention, to estimate the time, and to integrate semantic and visual dimensions has been documented.

Numerous epidemiological studies showed a relationship between short sleep and health risks. The studies of sleep restriction have shown a number of alterations of physiological parameters such as reduction of glucose tolerance, increased blood pressure, activation of the sympathetic nervous system, and increased inflammatory markers [17]. In recent years, a relationship between shortened sleep duration and increase in body mass index (BMI) in both adults and children has been documented in different countries. Cross-sectional studies have all shown a relationship between sleep and obesity. Similar evidence supports an association between short sleep/insomnia and the risk of developing diabetes and hypertension.

6.5 Hypersomnias

Hypersomnia is defined as excessive daytime sleepiness; in other words, it is the inability to stay alert and awake during the day. It can be associated with an increase in total daily amount of sleep, or it can consist of unintended sleep attacks, above all in boring and monotonous situations. Sleepiness may vary in severity and, when intense, can be the cause of dangerous accidents during actions requiring the constant, active participation of the subject.

Narcolepsy is the most relevant neurological disorder characterized by hypersomnia.

Key Facts

- **Terminology and definitions** – Narcolepsy with cataplexy, narcolepsy without cataplexy, narcolepsy/cataplexy syndrome, Gelineau syndrome, primary hypersomnia, narcolepsy with hypocretin deficiency.
- **Clinical features** – Narcolepsy is characterized by the presence of one or more of the following: excessive daytime sleepiness (EDS), cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, disrupted nocturnal sleep.
- **Diagnostic markers**
  - **CSF** hypocretin-1 dosage of ≤110 ng/L
  - **Genetics** – HLA DQB1*0602 allele in more than 90 % of patients with narcolepsy-cataplexy and in 40–50 % of patients with narcolepsy without cataplexy.
  - **Imaging (CT/MR)** – ns.
  - **Neurophysiology** – Polysomnography: disrupted nocturnal sleep structure; Multiple Sleep Latency Test (MSLT): average sleep latency ≤8 and 2 or more REM sleep onset periods [SOREMPs].
- **Top differential diagnoses** – Idiopathic hypersomnia with or without prolonged sleep time, recurrent hypersomnia, hypersomnia due to a sleep-related breathing disorder, behaviorally induced insufficient sleep syndrome, drop attacks, akinetic seizures, psychogenic nonepileptic seizures.
- **Principles of tretment and Prognosisw** – Modafinil, methylphenidate, sodium oxybate, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and selective noradrenalin reuptake inhibitors (SNRIs); Behavioral Treatment. Narcolepsy is a chronic disorder. EDS and cataplexy may improve with ageing, but disrupted nocturnal sleep may worsen.

6.5.1 Narcolepsy

6.5.1.1 Demographics and Clinical Features

The prevalence of narcolepsy with cataplexy ranges 25–50 per 100,000 people, 1/2000 in Europe and North America. Men with a slightly greater frequency than women. The age of onset can vary from infancy to the sixties and has a bimodal distribution with two peaks: a broader one at 15 years of age, and a smaller one at 36.

Narcolepsy is characterized by the presence of the following symptoms [1, 22]

- Excessive daytime sleepiness (EDS). "Naps" are typically brief (15–30 min) and refreshing. Even if brief, they are often associated with dream states.
- Cataplexy is the most specific symptom of narcolepsy, manifesting in about two thirds of cases within 5 years of EDS onset. It occurs in 60–90 % of narcoleptic patients and consists of the reduction or loss of muscle tone, with the exception of respiratory muscles and, usually, oculomotor muscles. It is triggered by emotional factors. During a cataplectic attack, usually lasting from few seconds to minutes but not usually more than 5 min, consciousness remains intact.
- Hypnagogic or hypnopompic hallucinations are reported in 40–80 % of narcoleptics, and can be auditory, visual, or tactile.
- Sleep paralysis occurs in 20–50 % of narcoleptics. It consists in the incapacity to move or speak voluntary, while breath is normal, either upon falling asleep or waking up from REM sleep. The phenomenon is interrupted if the subject is touched or by environmental noise.
- Disrupted nocturnal sleep – About 30–50 % of patients have fragmented nocturnal sleep. Narcoleptic patients fall asleep rapidly, but may complain of difficulty maintaining sleep.

6.5.1.2 Diagnostic Markers

CSF In 85–90 % of patients affected by narcolepsy with cataplexy, low hypocretin-1 CSF values may be found (≤110 ng/L) or hypocretin-1 absence; the percentage is lower (10–20 %) in patients with narcolepsy without cataplexy.

Genetics The HLA DQB1*0602 allele is found in more than 90 % of patients with narcolepsy-cataplexy and in 40–50 % of patients with narcolepsy without cataplexy but only in 12–38 % of healthy subjects.

Imaging (CT scan; MRI): ns.

Neurophysiology PSG: increase in stage N1, decrease in stage N3 and sleep fragmentation.

Multiple Sleep Latency Test (MSLT) – sleep latency ≤8 min and 2 or more REM sleep onset period (SOREMP).

Pathology Selective loss of orexinergic neurons of the lateral hypothalamus.

6.5.1.3 Top Differential Diagnoses

Idiopathic hypersomnia with or without prolonged sleep time, recurrent hypersomnia, hypersomnia due to a sleep-related breathing disorder, drop attacks, akinetic seizures, psychogenic non-epileptic seizures.

6.5.1.4 Principles of Treatment

Modafinil (100–400 and up to 600 mg/day) is currently one of the very few drugs whose efficacy in treating EDS has been proven in class I studies [23, 24]. It is little effective on cataplexy.

Sodium oxybate is useful for the treatment of EDS, but above all it is very effective on cataplexy at a dose of 3–9 g/night in two doses. It is currently the first-line therapy for cataplexy.

Second-line treatments: Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitors (significant reduction of cataplectic attacks in 50–100% of patients); Selective Noradrenalin Reuptake Inhibitors.

The efficacy of IVIg is controversial.

Behavioral treatment.

For disrupted nocturnal sleep: benzodiazepines, such as triazolam (0.125–0.25 mg), and non-benzodiazepine hypnotics (zolpidem, zopiclone, zaleplon).

6.5.1.5 Prognosis

Narcolepsy is a chronic disorder. EDS is the onset symptom in the majority of patients; cataplexy usually manifests itself within 1–5 years from the onset; sleep paralysis as well as hallucinations appear within 2–7 years. Symptoms continue lifelong, even though EDS and cataplexy often become less severe with aging and after retirement. Instead, disrupted nocturnal sleep worsens with age.

6.6 Restless Leg Syndrome (RLS)

Key Facts

- **Synonyms** – Ekbom's syndrome, restless leg syndrome, WED – Willis-Ekbom disease.
- **Clinical features** – Restless legs syndrome is a common sensorimotor disorder with a circadian rhythmicity defined by an uncontrollable urge to move the legs that worsens during periods of inactivity or at rest in the evening, resulting in sleep disruption.
- **Diagnostic markers**
  - **Blood** low ferritin levels in selected cases.
  - **CSF, imaging (CT/MR)** – ns.
  - **Genetics** – 60 % of cases of RLS are familial; several genetic linkages and four causative genes have been identified.
  - **Neurophysiology** – Polysomnography: fragmentation and reduced sleep efficiency, elevated periodic limb movements.
- **Top differential diagnoses** – Akathisia, neuropathy, nocturnal leg cramps, painful legs and moving toes, chronic venous insufficiency.
- **Principles of treatment** – Ropinirole, pramipexole, rotigotine, opioids, tramadole, methadone, clonazepam, levodopa, iron salt, gabapentin, pregabalin.
- **Prognosis** – RLS severity can worsen until the seventh or eighth decade of life, but may actually lessen in old age. In about two thirds of RLS patients, the symptoms progress over time, but do not increase the risk of all-cause mortality.

6.6.1 Demographics and Clinical Features

Two to 15 % of the world's population may experience symptoms of RLS.

RLS usually progresses slowly to daily symptoms and severe disruption of sleep after 50 years of age. Individuals with familial RLS tend to have onset of symptoms before age 45 years. Women are affected more commonly than men (2:1).

The main clinical features of RLS include [1]: (a) intense and irresistible urge to move the legs, usually associated with sensory symptoms (paresthesia or dysesthesia); (b) motor restlessness and agitation, with movements providing relief to the feeling of intense and irresistible urge to move the legs; (c) exacerbation of symptoms with rest; and (d) worsening in the evening, at bedtime, and/or in the early hours of the night.

RLS can severely interfere with the ability to initiate or maintain sleep, causing insomnia with particularly severe emotional disturbance leading to anticipatory anxiety, nervousness, and depression. The symptoms are usually bilateral but can occur predominantly on one side or with an involvement of the upper limbs.

RLS is frequently associated with periodic limb movements (PLM) during sleep, characterized by stereotyped, periodic muscle jerks (movements of extension of the big toe and dorsiflexion of the ankle lasting 0.5–5 s and occurring every 20–40 s), in one or both lower limbs. PLM tend to cluster in episodes, usually during the beginning stages of NREM sleep.

Blood Low ferritin levels (<50 mcg/L) in selected cases.

CSF, Imaging (CT scan; MRI) – ns.

Genetics Up to 60 % report a positive family history. Investigations of single families with RLS have suggested an autosomal dominant mode of inheritance with variable expressivity. Genome-wide association studies identified six genetic variants including MEIS1 and BTBD9 with potential relationships with iron metabolism [25].

Neurophysiology
Polysomnography: Reduction of total sleep time, long sleep latency, disrupted nocturnal sleep

structure, and elevated number of periodic leg movements – PLM-related arousals.

Pathology CNS pathology of RLS demonstrates reduced iron stores

6.6.2 Top Differential Diagnoses

Akathisia, neuropathy, nocturnal leg cramps, painful legs and moving toes, chronic venous insufficiency, radiculopathy.

6.6.3 Principles of Treatment

Pharmacological therapy is considered the most efficient form of treatment for RLS patients. Dopaminergic agents (e.g., pramipexole, ropinirole, levodopa-carbidopa, and rotigotine), benzodiazepines (e.g., clonazepam), opioids, anticonvulsants (e.g., gabapentin and pregabalin), and iron salt are commonly used.

6.6.4 Prognosis

As a general rule, RLS severity can worsen until the seventh or eighth decade of life, but may actually lessen in old age. In about two thirds of RLS patients, the symptoms progress over time. The severity of symptoms in patients with RLS ranges from mild to intolerable. In addition to being experienced in the legs, sensations also may occur in the arms or elsewhere. RLS symptoms are generally worse in the evening and night and less severe in the morning.

While RLS may present early in adult life with mild symptoms, by age 50 years it usually progresses to severe, daily disruption of sleep leading to decreased daytime alertness. RLS is commonly associated with reduced quality of life.

Patients with RLS and PLM may have an increased risk for hypertension. PLM is associated with an autonomic surge and an increase in blood pressure. Patients may also be more prone to headaches (migraine and tension-type). The headaches are probably secondary to sleep disturbances associated with RLS and PLM. Learning and memory difficulties have also been associated with RLS, presumably secondary to disrupted nocturnal sleep. Augmentation is defined as a worsening of RLS symptoms that occur after starting a medication to treat RLS. Particularly with dosage increases, RLS symptoms may occur earlier in the day, spread to body parts other than the legs, be more intense, and begin after a shorter period of rest or inactivity than before treatment.

Augmentation appears to occur most frequently with levodopa/carbidopa but also with pramipexole or ropinirole.

In terms of the influence of RLS on mortality risk, there have been conflicting reports. In four independently conducted large prospective cohort studies from Germany and the USA, RLS did not increase the risk of all-cause mortality [26].

There have been 20 cross-sectional epidemiological studies that have looked at the relationship between RLS and hypertension, heart disease and stroke. Of these 20 studies, 15 suggested an increased risk of hypertension, cerebrovascular disease, or heart disease in patients with RLS/PLM [27].

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Viral Infections of the Nervous System

7

Enrico Marchioni and Giulia Berzero

Abbreviations

ADEM, acute disseminated encephalomyelitis; APME, acute postinfectious measles encephalomyelitis; CHIKV, chikungunya virus; CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein–Barr virus; GCN, cerebellar granule cell neurons; HAART, highly active antiretroviral therapy; HCT, hematopoietic cell transplant; HH6, human herpesvirus- 6; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; IRIS, reconstitution inflammatory syndrome; JCV, JC Virus; JEV, Japanese encephalitis virus; MIBE, measles inclusion body encephalitis; MR, magnetic resonance; MV, measles virus; N.s., nonspecific; PME, primary measles encephalitis; PML, progressive multifocal leukoencephalopathy; PTLD, posttransplant lymphoproliferative disorders; SSPE, subacute sclerosing panencephalitis; TBEV, tick-borne encephalitis virus; VZV, varicella zoster virus; WNV, West Nile virus.

7.1 Encephalitis

Encephalitis is an inflammation of the brain parenchyma caused by a specific pathogen or by an antibody-mediated autoimmune mechanism.

Encephalitides with a known etiology account for 30–60 % of the total [1, 2]. Viruses are the most frequent cause of encephalitis in immunocompetent individuals [2], but the clinical phenotype may be nonspecific and similar to the one seen in other forms with an autoimmune pathogenesis. In the early stages of the disease, when an infectious origin is suspected but etiological data are still to be collected, a multidisciplinary collegial assessment of the patient can be very useful, in accordance with the diagnostic and therapeutic work-ups available in literature [3]. Encephalitis caused directly by viruses have, in fact, to be differentiated from those induced by an autoimmune process (referred to as ADEM or post-/parainfectious syndromes), which have a different treatment and carry a different prognosis. Still, there remains a large proportion of cases that cannot be diagnosed on the basis of current knowledge.

The aim of this chapter is to illustrate the information currently available with regard to the main issues in determining the prognosis "quoad vitam" and "quoad valetudinem" of viral encephalitides, and to distinguish clearly, within the same disease, between the forms of immunocompetent and immunocompromised individuals.

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7.1.1 Prognosis

Current literature is lacking reliable data regarding the prognosis of viral encephalitides. The few published systematic studies of forms of encephalitis caused by specific pathogens were retrospective and conducted on small samples; as a result, the available data allow only very approximate predictions of survival and functional outcome.

Overall, the prognosis of viral encephalitides depends on three main factors: (1) the neurotropism of the virus, (2) the immune status of the host, and (3) the existence (or otherwise) of an etiological treatment.

7.1.2 The Effects of Neurotropism

In the case of viruses with very selective brain neurotropism, such as Herpes Simplex virus (HSV) and Human Herpesvirus- 6 (HH6), the encephalitis presents a rather stereotypic phenotype. Conversely, other viruses, such as varicella zoster virus (VZV) and cytomegalovirus (CMV), whose mechanism of action is linked to either a vasculitis or an ependymal damage, cause multifocal brain and spinal cord lesions whose distribution is unpredictable.

Regardless of the causative agent, the prognosis is linked to the occurrence of two important and mutually independent events: epileptic seizures and myelitis. The event of seizures or status epilepticus during acute infection can significantly affect the patient's chances of survival and the persistence of residual deficits, as well as the quality of life in the long term. All the herpes viruses, but HSV and HH6 in particular, which electively target the temporal lobe and the limbic system (Fig. 7.1), are highly epileptogenic, and the seizures are often drug-resistant. Myelitis is a complication that can impact greatly on functional outcome. Although it is almost always possible, the chances of it occurring are much higher for viruses such as VZV, West Nile (WNV), and enteroviruses. The enteroviruses and WNV, for example, are known to affect the anterior horn cells, causing generally irreversible flaccid and amyotrophic paralysis.

7.1.3 The Immune Status of the Host

The patient's immune status is a fundamentally important aspect that must be taken into consideration from the very early stages of the disease, because it will help to indicate the set of aetiologies within which the patient's condition can most likely be framed.

Immunodeficiency occurs in four main clinical situations: HIV infection, cancer, bone marrow and organ transplants, and immunomodulatory therapies. Old age has to be considered a condition of immune depression, per se. In all the aforementioned conditions, the nervous system is particularly vulnerable both to opportunistic infections and to infections that commonly affect immunocompetent individuals.

The relations between immunodeficiency, underlying disease, and neurotropism of viruses are highly complex. Some opportunistic infections are known to occur only in a specific setting of immunosuppression, or in a specific phase of a given disease. Still, in only a few select cases has the experience of recent years been translated into accurate definitions of the risk factors, clinical and biological profiles, survival rates, and functional outcomes associated with a given form. To date, the best defined models are those of HH6 limbic encephalitis in posttransplant patients and progressive multifocal leukoencephalopathy (PML) in HIV infection and treatment with monoclonal antibodies, having a very different prognosis in the two settings.

Regarding the characteristic of the host that can adversely affect prognosis—besides age, a history of cancer and immunosuppressive treatments [4]—the presence of cerebral edema, coma, status epilepticus, thrombocytopenia, and the need for mechanical ventilation have also been reported [4, 5].

7.1.4 Antiviral Therapies

The antiviral and antiretroviral treatments introduced over the past two decades have changed the natural course of certain forms of encephalitis,

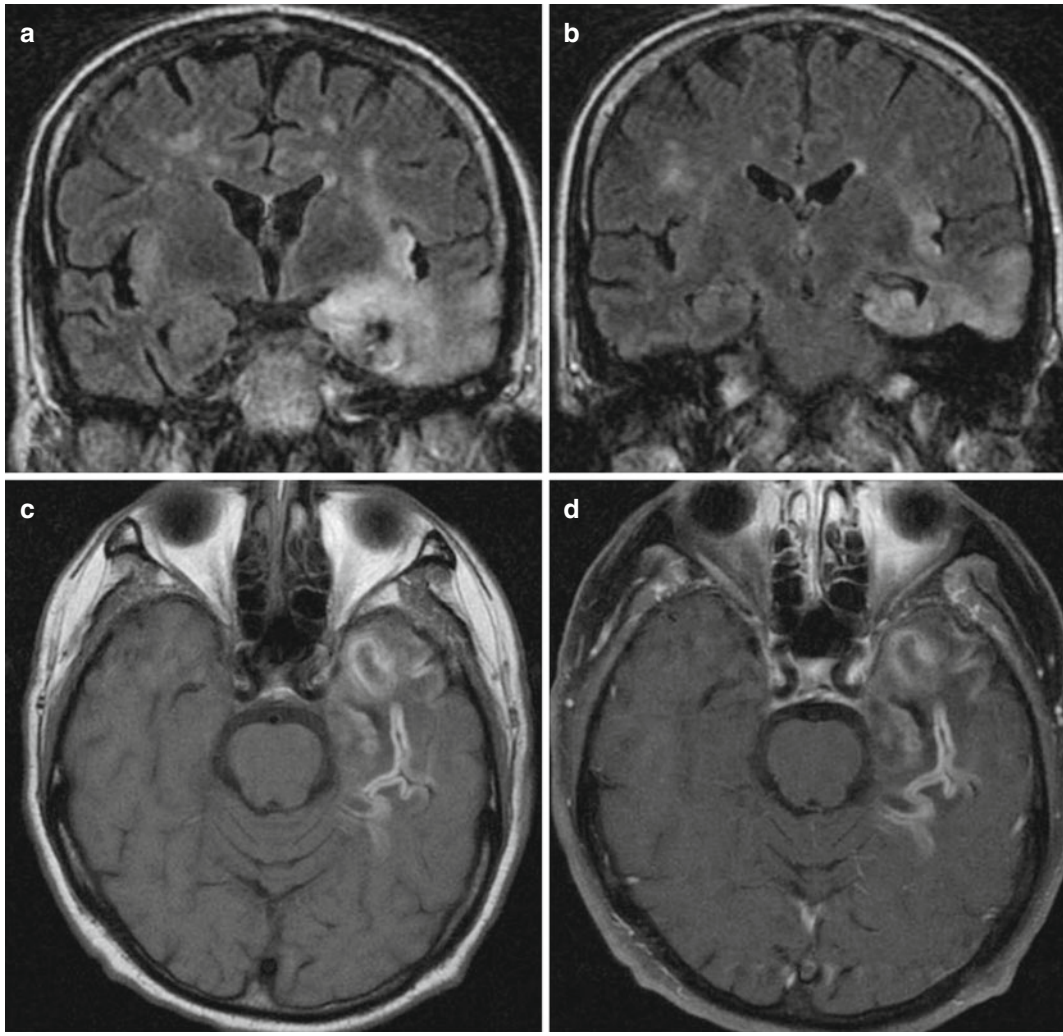

Fig. 7.1 Herpes simplex encephalitis, subacute stage. Coronal FLAIR images (**a**, **b**) show dishomogeneous hyperintensity in the left temporal medial region and in the left insula. Note the mild enlargement of the temporal horn. In (**c**, **d**), T1-weighted images without (**c**) and with contrast medium (**d**) show cortical hyperintensity due to laminar necrosis, with hemorrhage in the left temporal lobe. No definite enhancement was present.

in particular, herpes simplex encephalitis and all the HIV-related complications. Estimated survival rates have increased significantly, and the frequency of medium- to-long-term complications has fallen. Unfortunately, however, there still exist many forms of encephalitis for which there is no etiological treatment and whose outcome is determined essentially by variables related to the host and by the symptomatic treatment.

7.2 Herpesviruses

Herpesviruses are a common cause for severe acute and chronic neurological disease of the central nervous system (CNS), either during primary infection or following reactivation from a latent state. Especially in the immunosuppressed, the infection can take a life-threatening course, and diagnosis can be challenging, due to the presence of atypical clinical and instrumental

findings [6]. Therefore, the early detection of herpesvirus-associated neurological diseases should have high priority.

In immunocompromised hosts, in whom herpesviruses can undergo systemic reactivation, it is of capital importance to perform PCR CSF/serum ratio to distinguish active CNS compartmental viral replication from systemic responses.

In this chapter, we will consider the neurological diseases caused by six neurotropic herpesviruses: herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus-6 (HH6).

7.3 Herpes Simplex

Key Facts

- **Terminology and definition** – Species: *Herpes simplex virus type 1 and 2 (HSV-1 and HSV-2)*; genus: *Simplex virus*; family: *Herpesviridae.*
- **Epidemiology** – HSE is the most common form of sporadic viral encephalitis in the general population. HSVs infect via mucosal surfaces or damaged skin. Primary infection with HSV-1 usually occurs during childhood or adolescence, and is asymptomatic or results in gengivostomatitis. After primary infection, HSV-1 establishes latency in the neurons of the trigeminal ganglion, and can undergo reactivation with oral mucocutaneous shedding.
- **Clinical features** – The most frequent clinical features include fever, headache, aphasia, seizures, and alterations of consciousness, personality, and behavior, mimicking acute psychiatric conditions.
  HSV-2 can also be responsible for a form of benign, recurrent, lymphocytic meningitis (Mollaret's meningitis).
- **Diagnostic markers**
  - **CSF** – inflammatory changes in >95 % of cases.
  - **PCR for HSV-1 DNA** – very sensitive (98 %) and specific (94 %).
  - HSV CSF/serum antibody ratio may be helpful if > 1 week into therapy.
  - **Imaging** – Monolateral or bilateral temporoinsular hyperintensity (MR-FLAIR and T2W images); hemorrhagic foci.
- **Prognosis** – Neurologic sequelae in surviving patients are often severe, including focal deficits, seizures, and neuropsychological changes. Untreated, mortality approaches 70%.
- **Principles of treatment** – Intravenous acyclovir 10 mg/kg every 8 h for 14–21 days. Early recognition of the infection is critical since a delay in therapy is associated with increased morbidity and mortality. In the immunocompromised, HSV resistance to acyclovir is a serious concern, affecting about 5–25% of patients receiving long-term antiviral prophylaxis.

7.3.1 Prognosis

7.3.1.1 Mortality and Disability

Although the prognosis for patients with HSE has been dramatically improved by the availability of specific antiviral therapy, neurologic sequelae in surviving patients are often severe, including focal deficits, seizures, and neuropsychological changes. If untreated, mortality approaches 70 %.

The table below summarizes the prognostic factors for HSE.

Prognostic factors (predictors of poor outcome)
Older age
Depressed level of consciousness before the onset of therapy
Delay of >2 days between admission to the hospital and initiation of acyclovir
Simplified Acute Physiology Score II ≥27 at admission
Disorientation
Low albumin levels
Low sodium levels
Abnormal early CT scan

Immunocompetent Hosts

In immunocompetent hosts, HSE mortality is estimated between 10 and 25 %, despite adequate treatment; about half of the deaths are attributable directly to encephalitis and another half to infectious complications.

Among survivors, the overall incidence of neurologic sequelae is 30–70 %, ranging from mild/moderate (20–50 %) to severe (10–20 %) [7, 8]. The most common long-term sequelae are represented by memory impairment (69 %), anosmia (65 %), personality and behavioral changes (45 %), dysphasia (41 %), and epilepsy (24 %) [7]. The severity of the amnesia appears to correlate with the presence of bilateral medial limbic (hippocampal) damage and with its severity, detected by MRI.

Overall, only 14–48 % of the patients regain a premorbid level of functioning.

About 87 % of the survivors are eventually readmitted to the hospital due to epilepsy, infections (other than HSE), or neuropsychiatric conditions [9].

Immunocompromised Hosts

Although HSE is most commonly seen in immunocompetent hosts, cases of HSE in the context of immunosuppression such as HIV infection, cancer, solid organ or bone marrow transplantation have now been reported. In this setting, HSE presents with atypical clinical and instrumental findings, making diagnosis of the condition particularly challenging. This may possibly contribute to the high morbidity and mortality observed in this cohort [6].

Cancer

HSE has been reported in individual patients with cancer, with a majority of cases occurring shortly after brain irradiation. Additional sources of immunosuppression include chemotherapies and corticosteroids . However, estimates of the incidence of HSE in people with cancer compared to the general population are not available.

References	*No of cases*	*Mortality*	*Residual Disability*
Graber, 2011 [10]	31	20 (65 %)	Not available

HIV infection

Most cases of HSE in HIV-infected patients date back to the pre-HAART[a] era, occurring in association to CMV encephalitis. In this setting, mortality was extremely high, and diagnosis mainly autoptic. Latest reports indicate a mortality of about one-quarter or less, comparable to that of the general population.

Solid organ transplantation

In solid organ transplant recipients, HSV-systemic reactivation may be seen in the first post-transplant month, in the absence of prophylaxis.

Still, HSE rarely occurs; only a few cases after renal transplantation are reported in literature.

Bone marrow transplantation

Up to 25 % of patients who undergo allogenic stem cell transplantation suffer from severe neurological complications involving the CNS, frequently infections, which are associated with a poor outcome. The leading causative organisms of CNS infections in patients with malignancies are *Toxoplasma gondii* and fungi; viral infections have less frequently been reported.

References	*No of cases*	*Mortality*	*Residual Disability*
Schmidt-Hieber, 2011 [11]	4	1 (25 %)	1 (25 %)
Wu, 2013 [12]	5	3 (60 %)	1 (20 %)

Monoclonal antibodies

HSE has rarely been reported in patients receiving monoclonal antibodies for rheumatologic disorders or multiple sclerosis. In this setting, HSE retains a relatively good prognosis.

	References	*No of cases*	*Mortality*	*Residual Disability*
TNF-α inhibitors (rheumatologic disorders)	Bradford, 2009 [13]	3	0	2 (67 %)
Natalizumab (multiple sclerosis)	Fine, 2013 [14]	11	2 (18 %)	3 (27 %)

[a]*HAART* highly active antiretroviral therapy

7.4 Varicella Zoster

Key Facts

- **Terminology and definitions** – Species: *Varicella zoster virus* (VZV) or *Human herpesvirus 3* (HHV-3); genus: *Varicellovirus*; family: *Herpesviridae.*
- **Epidemiology** – Primary infection results in varicella (syn.: chicken pox). Viral transmission occurs by direct contact with skin lesions or by respiratory aerosols from infected individuals. After varicella resolves, VZV becomes latent in the peripheral nervous system and persists throughout the lifetime of the host.
- **Clinical features** – Neurological complications caused by VZV can occur either during primary infection or following reactivation, and can be caused by direct viral invasion or by vasculitis. They all can course with or without cutaneous rash.
  - **Acute cerebellar ataxia** 1/4000 children with varicella, with headache, vomiting, and mild cerebellar dysfunction.
  - **Encephalitis** without vasculopathy can affect both immunocompetent and immunosuppressed patients with nonspecific clinical features.
  - **Large vessel unifocal granulomatous arteritis** usually affects immunocompetent elderly individuals; the typical presentation is headache and hemiplegia occurring in patients with a recent history of herpes zoster ophthalmicus.
  - **Small vessel multifocal vasculopathy** usually occurs in severely immunocompromised patients (AIDS, lymphoproliferative disorders) and consists of subacute multifocal neurological deficits accompanied by headache, fever, mental changes, and seizures.
  - **Postzoster myelitis:** Sensory–motor dysfunction in the same spinal cord segment as in the cutaneous rash. Immunocompromised patients are at increased risk, and the syndrome is well-described in patients with AIDS.
- **Diagnostic markers**
  - **CSF**: moderate inflammatory changes.
  - **PCR for VZV** in acute cerebellar ataxia, encephalitis, and vasculopathies.
  - **VZV CSF/**serum antibody ratio is significantly altered in vasculopathies.
  - **Imaging** – MR usually normal (acute cerebellar ataxia); normal or n.s. supra- or infratentorial T2 hyperintensities in white/gray matter (encephalitis); ischemic infarction with focal stenosis or occlusion of the affected vessel (large vessel arteritis); multifocal brain infarcts (small vessel multifocal vasculopathy).
- **Prognosis** – Potentially lethal in both immunocompetente and immunocompromised patients.

7.4.1 Prognosis

7.4.1.1 Principles of Treatment

Therapy of VZV neurological complications has to rely on the context of immunocompetence, the possible putative pathogenesis, and disease severity.

In the context of immunosuppression, therapy with intravenous acyclovir is always recommended.

7.4.1.2 Mortality and Disability

Varicella zoster reactivation in the CNS is associated with a variety of serious and potentially lethal complications in both immunocompetent and immunocompromised individuals. Prognosis depends on age, immunological status of the host, and clinical pattern [15, 16].

Acute cerebellar ataxia

Cerebellar ataxia associated with varicella is self-limited and has a favorable prognosis. Mortality is essentially zero, and deaths that occur are usually attributed to the development of nonneurologic complications. Still, a significant number of patients experience residual disability.

References	*No of cases*	*Mortality*	*Residual disability*
Connolly, 1994 [17]	26	0 %	Behavioral abnormalities (31 %); speech abnormalities (19 %)
Camacho-Badilla, 2008 [18]	37	0 %	Minor sequelae (54 %)

Encephalitis

During the last decades, the mortality for VZV encephalitis has ranged from 5 to 35 %.
The actual mortality rate is probably around 10–15 %, with good recovery expected in most cases.

References	*No of cases*	*Mortality*	*Residual disability*
De Broucker, 2012 [19]	20	3 (15 %)	Moderate to severe sequelae (41 %): cognitive impairment, sensory–motor deficits, ataxia

Large vessel unifocal granulomatous arteritis

The mortality rate is 20–25 %, with a high incidence of permanent neurologic sequelae among survivors (headache, focal deficits, coma).

Small vessel multifocal vasculopathy

Prognosis is usually unfavorable, characterized by high short-term mortality.

Myelitis

In immunocompetent hosts, the involvement of the spinal cord is subtle and usually followed by complete recovery. Conversely, in immunocompromised individuals, the infection is often severe, leading to partial or total cord transection with substantial neurologic sequelae, or even death.

7.4.1.3 VZV Neurologic Disease in Settings of Immunosuppression

HIV/AIDS patients

The larger series reports 34 cases of neurological complications due to VZV [20], including encephalitis (13 cases), myelitis (8 cases), radiculitis (7 cases), and meningitis (6 cases). Neurological manifestations often involved simultaneously several sites in the central and/or peripheral nervous system. Severe symptoms at onset and a lower CD4 cell count were associated with poorer outcome.

References	*No of cases*	*Mortality*	*Residual disability*
De La Blanchardiere, 2000 [20]	34	6 (18 %)	Severe sequelae (29 %), complete recovery (53 %)

Bone marrow transplantation

Although VZV reactivation during the first 24 months from bone marrow transplantation is a common event, VZV meningoencephalitis is a rare complication, often occurring after the suspension of antiviral prophylaxis. Few cases are reported in literature, some with fatal outcome.

References	*No of cases*	*Mortality*	*Residual disability*
Suzuki, 2012 [21]	1 + 12	2 (15 %)	Not available

Monoclonal antibodies

Few cases of CNS complications caused by VZV during treatment with monoclonal antibodies are reported: one fatal case of VZV vasculopathy with Adalimumab [22] and four cases of VZV meningitis with Natalizumab, with favorable outcomes [14].

7.5 Epstein–Barr

Key Facts

- **Terminology and definitions** – Species: *Epstein–Barr virus* (EBV); genus: *Lymphocryptovirus*; family: *Herpesviridae.*
- **Epidemiology** – EBV is one of the most widespread viruses, infecting over 90 % of human beings in the first decades of life. EBV is most frequently transmitted via saliva. Primary infection is asymptomatic or results in infectious mononucleosis; once the initial lytic infection is brought under control, EBV establishes latency in B cells.
- **Clinical features** – Complications caused by EBV can involve the central or peripheral nervous system and can occur shortly before, during, or after infectious mononucleosis, as well as following acute EBV infection in the absence of symptomatic mononucleosis.
  - **Aseptic meningitis** is the most common complication of primary EBV infection.
  - **Encephalitis** is characterized by nonspecific clinical features ranging from fever and headache, to seizures, personality changes, and coma.
  - **Myelitis** may sometimes accompany encephalitis.
  - EBV has also been associated with AIDS-related CNS lymphomas and posttransplant lymphoproliferative disorders (PTLD). These entities range from reversible lymphoproliferative disorders that recover with the suspension of immunosuppressants, to malignant aggressive lymphomas.
- **Diagnostic markers**
  - **CSF**: lymphocytic pleocytosis and mild elevation in protein levels.
    The value of PCR assessment for EBV infections is uncertain, as EBV DNA is often detected in the CSF in the absence of neurological symptoms.
  - **Imaging**: T2W hyperintensities in cerebral white and/or gray matter on MRI.
- **Prognosis** – Aseptic meningitis has self-limiting course. Enchefalitis has 10-20% mortality rate.

7.5.1 Prognosis

7.5.1.1 Principles of Treatment

No specific antiviral therapy is available for the treatment of EBV-related neurologic complications, and therapy is mainly supportive. Corticosteroids may be effective in selected cases.

7.5.1.2 Mortality and Disability

- *Aseptic meningitis:* Self-limiting course; usually resolves without neurologic sequelae.
- *Encephalitis*: Mortality of 10–20 %. Incidence of neurologic sequelae of 20–38 % in immunocompetent hosts.
- Most cases of *myelitis* occur in children and young adults, and eventually resolve without sequelae, although reports of long-term sensory–motor deficits exist.

7.6 Cytomegalovirus

Key Facts

- **Terminology and definitions** – Species: *Human cytomegalovirus* (CMV); genus: *Cytomegalovirus*; family: *Herpesviridae.*
- **Epidemiology** – Primary infection with CMV usually occurs early in life by direct contact with bodily fluids (saliva, urine, blood, vaginal secretions, or semen) and is asymptomatic or can manifest as infectious mononucleosis. After primary infection, the virus establishes latency and is able to undergo reactivation in the event of immunosuppression.
- **Clinical features** – CMV encephalitis usually presents with nonspecific signs of encephalopathy, such as lethargy, confusion, and seizures. Immunocompromised individuals are at increased risk for potentially fatal disseminated CMV infections that can involve the eye, cochlea, and the CNS. Rarely, CMV can induce myelitis or polymononeuritis.
- **Diagnostic markers**
  - **CSF** analysis and *PCR* for CMV.
  - **Imaging** – MRI reveals subependymal gadolinium enhancement and nonspecific white matter abnormalities on T2W images.
- **Prognosis** – CMV eningoencephalitis carries favorable prognosis in immunocmpetent patients. Prognosis s frequently poor in immunocompromised hosts.

7.6.1 Prognosis

7.6.1.1 Medical Therapy

Ganciclovir is the treatment of choice for systemic CMV infection. Second-line antiviral drugs include valganciclovir, cidofovir, and foscarnet.

7.6.1.2 Mortality and Disability

Immunocompetent Hosts

CMV meningoencephalitis in immunocompetent hosts is characterized by favorable prognosis: most cases are mild and resolve without sequelae, but even cases characterized by severe neurologic involvement present high rates of complete recovery and very low mortality.

Immunocompromised Hosts

In immunocompromised hosts, the prognosis of CMV-induced neurological conditions is frequently poor, depending upon the cause of immunosuppression and the response to antiviral medications. In this cohort, CMV encephalitis is most frequent in HIV/AIDS patients, while it is a rare event in transplant recipients.

HIV infection

CMV-associated neurologic conditions among patients with HIV/AIDS have become much less common and less severe in the HAART[a] era (prevalence <2 %). They usually occur in patients with very low CD4 cell counts (<50 cells/μL) and are often accompanied by CMV disease in other sites, such as retina, gastrointestinal tract, and blood. CMV encephalitis can either be diffuse, focal, assume the pattern of ventriculitis, or occur in the form of pseudotumoral mass.

References	*No of cases*	*Mortality*	*Residual disability*
Silva, 2010 [23]	9	3 (33 %)	Not available

A neuropathology study of HIV-infected patients reported 28 (17 %) cases of CMV encephalitis, most of them with *premortem* diagnosis of HIV dementia, showing that CMV may be an underestimated cause of neurocognitive disorders in the HIV population.

Bone marrow transplantation

CMV-related CNS disease after allogenic stem cell transplantation is a late-onset event and usually causes encephalitis in the absence of the other sites of CMV disease. It is associated with umbilical cord blood transplantation, severe and protracted T-cell immunodeficiency, recurrent CMV viremia treated with multiple courses of antiviral therapy, and ganciclovir-resistant CMV infection. In this context, mortality is extremely high, reaching 90 % of cases.

References	*No of cases*	*Mortality*	*Residual disability*
Reddy, 2010 [24]	2+9	10 (90 %)	Not available

Solid organ transplantation

Solid organ transplant recipients are at risk for invasive disease from CMV reactivation, usually occurring during the first year after completion of prophylaxis. Although CMV systemic reactivation is relatively frequent, isolated CNS disease induced by CMV rarely occurs. Prognosis is highly dependent on the general conditions and the presence of end-organ disease.

[a]*HAART* highly active antiretroviral therapy

7.7 Human Herpesvirus-6

Key Facts

- **Terminology and definitions** – Species: *Human herpesvirus-6* (HHV-6)*;* genus: *Roseolovirus*; family: *Herpesviridae.*
- **Epidemiology** – HHV-6 is ubiquitous and transmitted through respiratory and oral secretions. Primary infection usually occurs within 2 years of age, and in normal infants results in roseola (exanthema subitum). After primary infection, HHV-6 establishes latency in the salivary glands, brain, and white blood cells. Viral reactivation usually occurs in severely immunocompromised states, causing fever, hepatitis, pneumonitis, and occasionally encephalitis.
- **Clinical features** – In immunocompromised hosts, there is a recognized pattern of HHV6 encephalitis targeting the limbic lobes, producing amnesia, neuropsychiatric changes, seizures, and hyponatremia. Nonspecific patterns have also been rarely reported. In immunocompetent hosts, the occurence of HHV6 encephalitis is still debated. The few reported cases in literature might be the result of a diagnostic bias due to the presence of chromosomally integrated viral genome in the host cells, resulting in positive CSF PCR testing.
- **Diagnostic markers**
  - **CSF** – Mild pleocytosis and elevated protein levels.
  - **PCR for HHV-6** has a low positive predictive value (30 %), due to the presence of chromosomally integrated viral genome in about 2 % of the general population. In this scenario, it is of capital importance to value the PCR CSF/serum ratio, to confirm active specific CNS compartmental viral replication.
  - **Imaging** – In immunocompetent hosts, MRI findings are frequently nonspecific. Conversely, in patients with limbic encephalitis, MRI shows bilateral nonenhancing medial temporal lobe hyperintensities in the T2, FLAIR, and DWI.
- **Principles of treatment** – Ganciclovir is currently used as first-line therapy for HHV-6 encephalitis. Other drugs that proved efficacy *in vitro* include forscarnet and cidofovir.
- **Prognosis** – Variable outcome. Complete recovery is frequent.

7.7.1 Prognosis

7.7.1.1 Mortality and Disability

Immunocompetent Hosts

HHV-6 encephalitis is a rare entity in immunocompetent hosts, and there are only few cases reported in literature. Outcome is variable, as complete recovery is frequent, but fatal cases are reported too.

Immunocompromised Hosts

Among the immunocompromised, HHV-6 encephalitis is most commonly described in bone marrow transplant recipients; it is a rare event in solid organ transplant recipients and HIV-infected patients.

Bone marrow transplantation

HHV-6 reactivates between 2 and 6 weeks after transplantation in 40–50 % of hematopoietic cell transplantation recipients. Younger age, underlying malignancy, allogenic transplants, unrelated or gender-mismatched donors, receipt of anti-T-cell antibodies, and receipt of steroids have all been identified as risk factors for HHV-6 reactivation in the HCT recipients.

References	*No of cases*	*Mortality*	*Residual disability*
Zerr, 2006 [25]	48	Overall mortality 39 %; 25 % encephalitis, 14 % sepsis, organ failure	Lingering neurological compromise (18 %)
Seeley, 2007 [26]	9	Overall mortality 55 % (sepsis, GVHD, acute renal failure, venoocclusive disease)	Residual cognitive impairment (33 %)
Shimazu, 2013 [27]	11	Overall mortality 82 %; 18 % encephalitis, 64 % progression of malignancy, pulmonary disease	All survivors experienced cognitive deficits

Solid organ transplantation

Although systemic HHV-6 reactivation is a frequent event in the early phases after solid organ transplantation, only few cases of HHV-6 encephalitis are reported in literature after liver, lung, heart, or kidney/pancreas transplantation. Prognosis quoad vitam is commonly favorable in this cohort; no data are available on neurologic sequelae.

References	*No of cases*	*Mortality*	*Residual disability*
Vinnard, 2009 [28]	1 + 5	1 (17 %)	Not available

HIV infection

The role of HHV-6 in the pathogenesis of CNS disease in HIV patients remains unclear, as HHV-6 DNA is detected in the CSF of patients with HIV/AIDS and neurological disease in 2–30 % of cases, but CNS disease is finally attributed to other opportunistic pathogens.

Acute HHV-6 infection often presents with a rapidly fatal meningoencephalitis.

References	*No of cases*	*Mortality*	*Residual disability*
Corti, 2011 [29]	5	4 (80 %)	Good clinical recovery in the surviving patient

7.8 Progressive multifocal leukoencephalopathy (PML)

Key Facts

- **Terminology and definitions** – species: *JC Virus (JCV)*; genus: *polyomavirus*; family: *Polyomaviridae*.
- **Epidemiology** – Primary infection with JCV occurs early in life through inhalation, and is typically asymptomatic. Tonsillar lymphocytes infected with JCV carry virions to the kidney and bone marrow, which are thought to be the primary sites of latency. Despite the high prevalence of JCV infection in healthy adults, PML almost exclusively develops in immunocompromised individuals (AIDS, treatment with monoclonal antibodies).
- **Clinical features**
  - **Classic PML** – PML typically presents with subacute neurological deficits including altered mental status, motor/sensory/visual deficits, and ataxia. Lesions may occur anywhere in the CNS white matter, although they appear to spare the optic nerves and the spinal cord. The natural clinical course usually spans over weeks or months, resulting in dementia, blindness, paralysis, and finally coma and death.
  - **Inflammatory Progressive Multifocal Leukoencephalopathy (PML/IRIS)** – New onset or clinical worsening of PML has been described in the setting of recovery of the immune system (e.g., HAART); this phenomenon has been called immune reconstitution inflammatory syndrome (IRIS).
  - **JCV Infection of Cerebellar Granule Cell Neurons (GCN)** – Ataxia and cerebellar atrophy can occur in the absence of white matter lesions in the cerebellum.
- **Diagnosis**
  - **CSF** – PCR for JCV on CSF has sensitivity of 50–75 % and specificity of 98–100 %.
  - **Imaging** – Classic PML is characterized by one or more, nonenhancing, confluent, subcortical white matter hyperintensities on T2W/FLAIR images. Conversely, PML/IRIS is defined by enhancing, inflammatory lesions.
  - **Brain biopsy** – Has sensitivity of 64–96 % and specificity of nearly 100 %.
- **Principles of treatment**
  There is no specific antiviral therapy against JCV. Although anecdotal reports of response to various treatments are reported, all controlled studies have failed to show any efficacy of the drugs tested.
- The best treatment for PML is the restoration of the immune system, although it can lead to IRIS. In severe forms of IRIS, the use of steroids may be indicated.
- **Prognosis** – The natural clinical course of classic PML usually spans over weeks or months, resulting in dementia, blindness, paralysis, and finally coma and death.

7.8.1 Prognosis

7.8.1.1 Mortality and Disability

PML was originally described in patients with HIV/AIDS with very low CD4+ cell count. In recent years, PML has been increasingly reported in other cohorts, such as patients receiving immunosuppressors for hematologic malignancies, and patients receiving monoclonal antibodies.

HIV infection

The advent of HAART[a] has markedly reduced the incidence and the mortality due to PML in the HIV cohort. During the pre-HAART era, death was nearly universal, with an average survival of 2–4 months. Since the introduction of HAART, survival has improved significantly, with a 1-year probability of survival of 50 % or higher, compared with 5 % or lower in patients not receiving HAART. Still, patients surviving PML frequently experience irreversible neurological sequelae. Engsig [30] analyzed the incidence, clinical presentation, and outcome of PML in HIV-infected patients during the HAART era: a CD4 + cell count ≥50 cells/uL at the diagnosis of PML and a diagnosis of PML after 1997 were associated with reduced mortality. Only two patients had IRIS: both patients died at 40 and 59 days after the diagnosis of PML.

References	*No of cases*	*Mortality*	*Residual disability*
Engsig, 2009 [30]	47	74 %	Progression or stability of neurological symptoms (27 %); high degree of restitution or return to premorbid status (73 %)

Hematologic malignancies

The use of new antineoplastic agents, high-dose therapy with hematopoietic stem cell transplantation (HDT/HSCT), and monoclonal antibodies for lymphoproliferative disorders has led to a striking improvement in disease-free survival but also to a higher incidence of opportunistic infections, such as PML. A recent review [31] reports a mortality rate of 90 % in patients diagnosed before 1989 and treated with alkylating agents and/or radiotherapy for an advanced Hodgkin lymphoma, and a mortality rate of about 80 % in patients diagnosed from 1990 to 2004 receiving purine analogs (mortality 90 %) and high-dose therapy with HSCT (mortality 62.5 %) for a B-cell chronic lymphocytic leukemia or an aggressive non-Hodgkin lymphoma.

References	*No of cases*	*Mortality*	*Residual disability*
Garcia-Suarez, 2005 [31]	46	80–95 %	Only 5 patients survived (median survival — 12 months)

Solid organ and bone marrow transplantation

The risk factors, clinical spectrum, and incidence of PML among transplant recipients remain uncertain even though the transplant population is likely at a significant risk of developing PML.

A recent study [32] reported 69 cases of posttransplantation PML described in literature (44 solid organ transplants and 25 bone marrow transplants). Median survival following symptom onset was 6.4 months in solid organ versus 19.5 months in bone marrow recipients. Overall, transplant recipients were exposed to 42 different immunosuppressive drugs and various chemotherapeutic agents or monoclonal antibodies. One fatal case of IRIS is described.

	References	*No of cases*	*Mortality*	*Residual disability*
	Mateen, 2011 [32]	15 + 54	84 %	Not available

Monoclonal antibodies

A number of PML cases in patients receiving monoclonal antibodies have been reported and summarized in the following table [33].

	Rituximab	Natalizumab	Efalizumab
Target	Anti-CD20	Binds the α-4 integrin	Anti-CD11
Therapeutic indications	Rheumatoid arthritis, NHL[b], CLL[c]	Relapsing–remitting MS[e], Crohn's disease	Plaque psoriasis (withdrawn in 2009)
Number of confirmed cases of drug-associated PML (mortality)	57 (89 %)	13 (23 %)	3 (66.6 %)
Epidemiological estimate for drug-associated PML	1 in 4000, in patients with SLE[d]	1 in 1000	1 in 400 in patients who received ≥3 years of therapy

A recent study [34] analyzed the clinical outcome and the variables connected with survival of the first 35 postmarketing cases of natalizumab-associated PML. At the time of analysis (follow-up 6.8–4.5 months), 25 patients (71 %) had survived. Of the ten patients who died, five probably died of IRIS. Survivors were younger and had lower pre-PML expanded disability status scale scores and a shorter time from symptom onset to diagnosis, compared with individuals with fatal cases. Among survivors with at least 6 months follow-up, disability levels were evenly distributed among mild (16 %), moderate (36 %), and severe (48 %).

[a]HAART Highly active antiretroviral therapy
[b]NHL Non-Hodgkin lymphoma
[c]CLL Chronic lymphocytic leukemia
[d]SLE Systemic lupus erythematosus
[e]MS Multiple sclerosis

7.9 Measles

Key Facts

- **Terminology and definitions** – Species: *Measles virus (MV)*; genus: *Morbillivirus*; family: *Paramyxoviridae.*
- **Epidemiology** – Measles virus spreads between individuals through aerosolized respiratory droplets and enters the CNS through cerebral endothelial cells or infected monocytes.
  The CNS complications of measles (syn: rubeola) can occur within days of acute measles infection or may be delayed for weeks, months, or even years. While most forms affect immunocompetent hosts, measles inclusion body encephalitis affects mainly immunocompromised children.
- **Clinical features** – Measles can induce encephalitis in at least four different paradigms, each with a different pathogenesis: primary measles encephalitis (PME), acute postinfectious measles encephalomyelitis (APME), measles inclusion body encephalitis (MIBE), and subacute sclerosing panencephalitis (SSPE) [35]. (The main characteristics of measles encephalitides are summarized in Table 7.1).
- **Diagnosis**
  - **CSF** – Mild pleocytosis, normal/elevated proteins, increased gammaglobulins (SSPE). Other useful tools include CSF/serum antibodies ratio (MIBE, APME, SSPE) and RT–PCR for MV on CSF (PME).
  - **Imaging** – Cerebral T2 focal hyperintensities (PME); white matter multifocal T2 hyperintensities in brain and spinal cord (APME); normal at presentation, followed by edema, atrophy, and ventriculomegaly (MIBE); focal leukodystrophy, and diffuse cortical atrophy (SSPE).
  - **EEG** – High-amplitude bursts of periodic slow-wave complexes, accompanied by axial myoclonic spasms (SSPE); diffuse slow waves with disease progression.
- **Prognosis** – The CNS complications of measles are severe often resulting in disability or death.

Table 7.1 Measles encephalitides

	PME	APME	MIBE	SSPE
Clinical setting	Active measles infection	Recent measles infection, no longer active	Measles infection in immunocompromised children	Measles infection in the first 2 years of life
Time of onset after infection/vaccination	During the exanthema	Weeks to months	Within 1 year	From 3 to 20 years
Presence/absence of MV	Presence of infectious MV	No MV present	Persistence of infectious MV	Defective MV
Clinical signs	Fever, headache, altered mental status, seizures, weakness, rash	Weakness, sensory loss	Altered mental status, seizures, motor deficits, no/mild rash	Behavior changes, progressive dementia, myoclonus
Treatment	Antiviral drugs	Corticosteroids, IVIG, and plasmapheresis	Cessation of immunosuppressants (when possible), antiviral drugs	Symptomatic supportive care

7.9.1 Prognosis

7.9.1.1 Mortality and Disability

The CNS complications of measles are often severe, resulting in substantial disability or death. Prognosis varies according to clinical pattern [35].

Primary measles encephalitis (PME)
The prognosis for patients with PME is guarded. Of these patients, 10–15 % will die, and an additional 25 % will be left with permanent neurologic sequelae, including seizures and mental retardation.

Acute Postinfectious Measles Encephalomyelitis (APME)
Mortality related to APME is estimated around 10–25 %, depending on the age of the reports. Although some experience full recovery, about one-third of survivors are left with lifelong neurological sequelae, including severe retardation, motor impairment, blindness, and hemiparesis.

Measles Inclusion Body Encephalitis (MIBE)
MIBE affects mainly immunocompromised children with lymphoblastic leukemia, solid malignancies, HIV infection, or autoimmune diseases. The mortality rate associated with MIBE is approximately 75 %, with death generally occurring within weeks of onset of the illness. Those who survive this illness suffer considerable morbidity from neurologic abnormalities.

References	*No of cases*	*Mortality*	*Residual disability*
Mustafa, 1993 [36]	2+31	85 %	All surviving patients experienced neurologic sequelae, ranging from severe psychomotor retardation to moderate cognitive disability

Subacute Sclerosing Panencephalitis (SSPE)
SSPE is relentlessly progressive, with a fatal outcome in 95 % of affected individuals. The mean survival ranges from 1 to 3 years. In one study by Risk and Haddad [37], 41 % of affected individuals remained alive after 2 years of disease progression. Prashanth [38] has analyzed the clinical profile of 19 patients with a relatively "benign" course, who survived beyond 3 years. Clinical course of these patients included spontaneous stabilization, remissions, and relapses. There was spontaneous stabilization for 6 months to 6 years in 13 patients. Nine patients had temporary remissions in clinical status, which lasted from 6 months to 9 years. Ten patients received disease-modifying agents, without any discernible effects. Prolonged survival from 3 to 13.8 years was documented.

7.10 Arboviruses

Key Facts

- **Terminology and definitions**
  Arboviruses are transmitted to humans and other vertebrates by hematophagous arthropod vectors such as mosquitoes, biting midges, phlebotomine sand flies, and ticks.
- **Epidemiology** [39] – Japanese encephalitis virus (JEV) in SE Asia, Pacific Rim; West Nile virus (WNV) in North America, Africa, Europe, Asia, and Australia; Tick-borne encephalitis virus (TBEV) in Europe and Russia; Toscana virus in Europe; Chikungunya virus (CHIKV) in Africa, India, and SE Asia.
- **Clinical features**
  Arboviruses cause serious illness in humans, ranging from rash and arthritis to hemorrhagic fever and encephalitis. CNS diseases occur both in immunocompetent and immunocompromised hosts and are usually preceded by variable combinations of fever, headache, body aches, nausea, and vomiting. Encephalopathy and seizures are the most common neurological signs of the ensuing phase additional features include signs of dysfunction of the basal ganglia (dystonia, tremors, or rigidity), cranial nerves, or anterior horn cells (areflexia, flaccidity).
- **Diagnosis**
  - **CSF** – Lymphocytic (JEV) or neutrophil (TBEV) pleocytosis, normal/decreased glucose levels, and elevated protein levels. For etiologic diagnosis: IgM antibodies titers on CSF, and RT–PCR (WN, TBEV, Chikungunya).
  - **Imaging** – T2/FLAIR hyperintense lesions in thalami, basal ganglia, and brain stem.
- **Principles of treatment** – No antiviral drugs have been proven effective in the treatment of arboviral encephalitides in humans.
- **Prognosis** – Mortality rate: JEV = 20–30 %, CNS WNV = 10 %, TBEV = 20–60 % (Far East subtype) 2 % (European), CHKV = 10 %, Toscana virus usually causes benign diseases.

7.10.1 Prognosis

7.10.1.1 Mortality and Disability

Japanese Encephalitis Virus (JEV)

JEV is the leading cause of viral encephalitis in Asia (35,000–50,000 cases reported annually). JEV encephalitis is a particularly severe disease, with death sometimes occurring quickly after an initial fulminant phase. Overall, 20–30 % of hospitalized patients die, and half the survivors have neuropsychiatric sequelae [16]. Patients destined to recover tend to manifest improvement after 2–4 days of illness. Higher morbidity and mortality are found in individuals younger than 10 years or older than 65 years. Poor prognostic signs include a depressed level of consciousness, decerebrate posturing, increased intracranial pressure, multiple seizures, isolation of the virus from CSF, and low levels of JEV-specific IgM and IgG in CSF and serum.

West Nile Virus (WNV)

WNV infection manifests with neuroinvasive disease in <1 % of cases, with a mortality rate of about 10 % in affected patients. Increased age is the most important risk factor for the development of neuroinvasion and death; other risk factors include the presence of deep coma, impaired immunity, failure to produce IgM antibodies, and coexisting illnesses such as hypertension and diabetes mellitus. Survivors of WNV encephalitis often suffer long-term cognitive and neurological impairments, including muscle weakness, insomnia, depression, confusion, headache, and myalgia. A study by Weiss et al. [40] reports 19 cases of CNS involvement: 7 (37 %) recovered fully, 10 patients (53 %) recovered partially, and 2 died (11 %).

Tick-Borne Encephalitis Virus (TBEV)

TBE is a disease with a severe acute clinical course and considerable long-term morbidity. Traditionally, the disease caused by the Far East subtype of TBEV is thought to be more severe than that caused by the European subtype, with case-fatality rates of 20–60 %, compared with 1–3 %, respectively [16]. Neurologic sequelae have been identified in about 35–58 % of the patients with TBE, including decreased concentration and memory, emotional lability, aphasia, headache, tremor, and ataxia. Age, severity of illness in the acute stage, and low neutralizing antibodies titers at onset are associated with severe forms of disease, along with early CSF IgM response. Patients with severe disease may present incomplete recovery.

Chikungunya Virus (CHIKV)

CHIKV has been implicated in a number of outbreaks of painful polyarthralgia and myalgia in East and Southern Africa and Southeast Asia over the last 50 years. It was during one of the most recent outbreaks (La Réunion, 2005–2006) that the ability of CHIKV to cause encephalitis was first appreciated. In epidemics that have occurred since 2005, mortality associated with CHIKV infection has been described, with a case-fatality rate of about 1 in 1000, with most deaths occurring in neonates, elderly people, and in adults with underlying disorders. The common causes of death were heart failure, multiple organ failure, hepatitis, and encephalitis. The estimated mortality in patients with CHIKV infections of the CNS is around 10 %.

Toscana Virus

A recent review [41] summarizes 41 cases of Toscana virus infections of the CNS reported in literature; most patients (92 %) had a benign and self-limiting disease. Recovery is usually complete, and neurologic sequelae are uncommon.

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8 Bacterial, Fungal, and Parasitic Infections of the Central Nervous System

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Abbreviations

ART, artemether; ASE, acute schistosomal encephalopathy; CM, cerebral malaria; CSF, cerebrospinal fluid; CT, computed tomography; CT, congenital toxoplasmosis; ELBW, extremely low birth weight infants; HAART, highly active antiretroviral therapy; HAT, human African trypanosomiasis; IGRA, interferon gamma release assays; IV, intravenous; LP, lumbar puncture; NCC, neurocysticercosis; PCR, polymerase chain reaction; PES, pseudotumoral encephalic schistosomiasis; PZQ, praziquantel; SCS, spinal cord schistosomiasis; TB, tuberculosis; TBM, tubercular meningitis; TE, toxoplasma encephalitis; vp, ventriculoperitoneal; YO, years old.

8.1 CNS Bacterial Infections

8.1.1 Acute Bacterial Meningitis

Key Facts

- **Terminology and definitions** – Acute bacterial meningitis.
- **Clinical features** – Fever, severe headache, and stiffness of the neck (meningismus), with or without altered mental status.
- **Diagnosis**
  - **Blood** – Positive culture.
  - **CSF** – Positive culture.
  - **Imaging** – CT scan to predict intracranial hypertension.
- **Prognosis**
  - **Principles of treatment** – Antibiotics.
  - **Disability** – Mortality: 40–75 % in infants and older people.

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8.1.1.1 Terminology and Definitions

Meningitis is an infection involving the subarachnoid space causing an inflammatory reaction in the cerebrospinal fluid (CSF). Almost any bacterium gaining entrance to the body may produce meningitis by hematogenous spread, by extension from suppurative parameningeal foci (ears, sinuses), by head-penetrating trauma, or by neurosurgical procedures. The most common pathogens for community-acquired acute bacterial meningitis are by far *S. pneumonia* (50 %), *Neisseria meningitidis* (25 %), Group B Streptococci (13 %), and *Hemophilus influenzae* (7 %). *Listeria monocytogenes* (8 %) is now to be strongly considered in concomitant medical history of immunosuppression, alcoholism, diabetes, and liver and kidney severe dysfunction. Hospital-acquired meningitis may also be associated with *Staphylococcus aureus* and enteric Gram-negative bacilli.

8.1.1.2 Clinical Features

The classic presentation of bacterial meningitis is fever, severe headache, and stiffness of the neck (meningismus), with or without altered mental status. Approximately 50 % of meningococcal meningitis is characterized by an initial petechial rash.

8.1.1.3 Diagnosis

- **Blood cultures**: 2–3 samples (positive in 40–60 % of patients);
- *CSF* – Elevated spinal fluid pressure (>180 mm H_2O), neutrophils pleocitosis (85–90 %), protein higher than 45 mg/dL, low glucose level (<40 mg/dL), Gram stain and cultures of the spinal fluid, detection of bacterial antigens.
- *Computed tomography* (CT) to predict intracranial hypertension and the risk for brain stem herniation due to lumbar puncture (LP);
- *Chest X-Ray* is essential to disclose pneumonia or abscess; CT scan or MRI to detect the presence of paranasal sinusitis, mastoiditis.

8.1.1.4 Prognosis

Principles of Treatment

First, ensure that patients are hemodynamically and neurologically stable. Selected individuals may require hydric and hemodynamic support eventually in ICU. Empiric antimicrobials should be immediately administered preferably within 1 h, but after blood cultures are drawn. LP can be performed within 1–2 h of antibiotics, without significant loss of sensitivity for Gram stain and cultures. Empiric antibiotic therapy can then be modified according to microbiological data. Duration of therapy is generally 7 days for *N. meningitidis*, 10–14 days for *S. pneumonia*, except for the presence of persistent parameningeal foci of infections, and up to 21–28 days for *L. monocytogenes*, *S. agalactiae*, and Enterobacteriaceae.

Use of corticosteroid has been controversial. IV Dexamethasone 0.15 mg/kg every 6 h for 2–4 days before or with the first dose of antibiotics was associated with a relative risk of death of 0.4 and a relative risk of neurological sequelae of 0.6 when compared with patients who did not receive steroid, in particular in patients affected by *S. pneumonia* meningitis.

Mortality and Disabilities

Untreated bacterial meningitis is usually fatal. In infants and in older people, mortality is very high (from 40 to 75 %), especially for infants in developing countries, with 50 % of serious neurological sequelae of those who survive [1].

In adults, the prognosis also worsens in the presence of bacteremia, coma, seizures, and in the presence of other comorbidities.

Relatively few adult patients who recover from meningitis show residual neurologic problems.

Pathogen	Overall mortality rate in uncomplicated meningitis	Overall mortality rate in complicated meningitis	Residual disability essentially encountered in infants
N. meningitidis	6 %	13–32 %	9 % behavioral problem, 30 %
S. pneumoniae	13.5 %	24 %	neurologic deficits (seizures, hearing,
H. influenzae	0.9–9 %	–	language, mental, motor disorder)
L. monocytogenes	15–30 %	–	31 % (deafness, later seizures)
			25 % (deafness 6 %)

8.1.2 Brain Abscesses

Key Facts	
• **Terminology and definitions** – Brain abscesses. • **Clinical features** – Headache is the most common (70 %) symptom. – **Blood** – Positive culture in 10 % of cases. – **CSF** – Contraindicated. – **Imaging**: *CT scan*, *MRI.*	• **Prognosis** – **Principles of treatment** – Antibiotics ad neurosurgery. – **Disability** – Mortality 100 % before the advent of antibiotics.

8.1.2.1 Terminology and Definitions

Brain abscess is an intracerebral collection of pus that often presents as a mass lesion causing focal neurological deficits related to the area involved. Primary source is often cryptogenic; 50 % caused by contiguous spread from the middle ear, paranasal sinuses, or dental foci, 25 % occurs after hematogenous spread from the lung (bronchiectasis, abscess) or heart (endocarditis, congenital defects), and 10 % are exogenous (fractures of the skull, intracranial surgery). Brain abscesses affect males more than females and involve 30–40-year-old patients most commonly.

8.1.2.2 Clinical Features

Headache is the most common (70 %) initial symptom of intracranial abscess. Other symptoms by frequency are drowsiness and confusion, focal or generalized seizures, focal motor, sensory, or speech disorders, nausea, and vomit. Fever (50 %) and leukocytosis are not always present, and the course of the disease can be indolent but sometimes rapidly life-threatening.

8.1.2.3 Diagnostic Markers

Diagnosis is based on a high index of clinical suspicion in patients with risk factors. Common microorganisms involved in brain abscesses are streptococci (70 % of cases), mostly anaerobic or microaerophilic. Infection is often polymicrobial (60 % of cases) with the involvement of other anaerobes and Enterobacteriaceae (20–50 % especially *E. coli*, *Proteus*). Staphylococci are also common (20 %), especially after neurosurgery. In immunocompromised hosts, *Nocardia* spp. should be considered.

Blood – Positive cultures in 10 % of cases.

CSF – Spinal tap is generally contraindicated, because intracranial pressure is elevated in many patients.

CT and MRI – Are the most important diagnostic tools.

Chest X-Ray – Is mandatory to rule out pneumonia, bronchiectasis, as original foci of infection.

8.1.2.4 Prognosis

The advent of antibiotics, new imaging, and stereotactic drainage has decreased the mortality near to zero [2].

Principles of Treatment

Empiric high-dose parenteral antimicrobials may be indicated after a complete diagnostic evaluation with intensive support and, occasionally, neurosurgical intervention. A third-generation cephalosporin plus metronidazole (eventually plus vancomycine or amikacin) is an adequate approach to the early stage of abscess formation (cerebritis). Abscess larger than 2.5 cm should be aspirated before starting an empirical therapy. Treatment must be targeted on the antimicrobial susceptibility tests. The duration of therapy depends on clinical and neuroimaging monitoring, and several weeks of treatment is advised. Intracranial pressure

should be managed by the use of IV mannitol and dexamethasone 6–12 mg q6h.

Mortality and Disabilities

Prior to antibiotics and refinement of neurosurgical techniques, mortality approached 100 %. If the patient is comatose before appropriate treatment, mortality approaches 20–50 %; if the treatment starts when the patient is still alert, the range of mortality decreases to 5 and 10 %. Among the surviving patients, approximately 30 % complain of some neurological disorders, particularly of focal epilepsy.

8.1.3 Tuberculosis (TB)

Key Facts

- **Terminology and definitions** – *Mycobacterium tuberculosis*.
- **Clinical features** – TBM, tuberculoma myelitis. British Medical Council criteria for TBM.
- **Diagnosis**
  - **Skin**: Mantoux.
  - **Blood** – IGRA test.
  - **CSF** – Lymphocytic pleocitosis, low glucose level (<5 mg/dL). Positive culture or PCR.
  - **Imaging** – CT scan/MRI, tuberculoma, hydrocephalus, meningitis, vasculitis.
- **Prognosis**
  - **Principles of treatment** – Antituberculous drugs, surgery in case of hydrocephalus.
  - **Disability** – Mortality, 20–50 %. Residual deficits, 20–50 %.

8.1.3.1 Terminology and Definitions

TB is one of the most common infections by a single agent all over the world, and is second only to HIV. It is caused by *Mycobacterium tuberculosis* that is acquired through inhalation of airborne droplet nuclei with a possible secondary dissemination to other organs, such as CNS. CNS TB may affect immunocompetent hosts, but more commonly it involves immunocompromised ones, and in particular children (Fig. 8.1). CNS TB is five times more common in HIV-positive compared to HIV-negative patients.

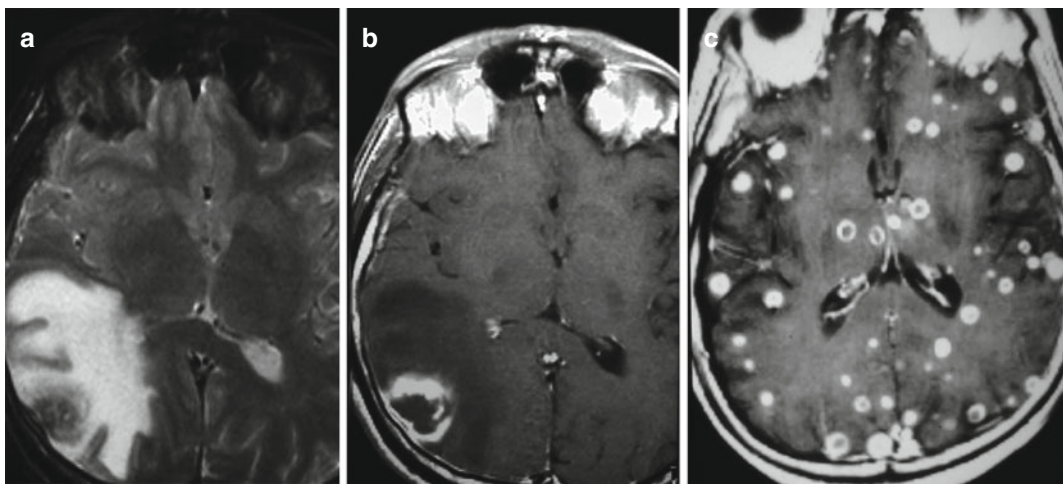

Fig. 8.1 Tuberculosis. Axial T2-weighted image (**a**) and axial T1-weighted image after contrast medium (**b**) in one patient with moderate immunodeficiency demonstrate a single right occipital–temporal granuloma characterized by a nodular necrosis associated with abundant perilesional edema and mass effect on the right ventricle. In another completely immunodeficient patient, a miliary tuberculosis is clearly evident in the axial T1-weighted image after contrast medium (**c**)

8.1.3.2 Clinical Features

- TBM
- Tuberculoma
- Myelitis

The British Medical Council has established clinical criteria for the severity of TBM: stage I—fully conscious and no focal deficits; stage II—conscious but with inattention, confusion, lethargy, and focal neurological signs; stage III—stuporous or comatose, multiple cranial nerve palsies, or complete hemiparesis or paralysis.

8.1.3.3 Diagnosis

Skin Intradermal reaction of Mantoux

Blood IGRA test (low sensitivity)

CSF Lymphocytic pleocitosis, low glucose level (<5 mg/dL). Culture for *Mycobacterium tuberculosis*, PCR (low sensitivity)

Cerebral CT scan/MRI Tuberculoma, hydrocephalus, meningitis, vasculitis

8.1.3.4 Prognosis

Principles of Treatment

The standard approach to CNS tuberculosis includes an initial 2-month induction therapy regimen, including isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 7–10 additional months of isoniazid and rifampin as maintenance therapy for an isolate that is sensitive to these agents. Treatment with corticosteroids is strongly recommended in CNS TB, in particular, because it reduces mortality from TBM. In case of severe hydrocephalus, surgical treatment is necessary to reduce the mass effect of tuberculomas and to drain brain abscesses.

Mortality and Disability

The clinical stage at diagnosis, the immunological status of the host, and antimicrobial resistance pattern of the strains are the main determinants of prognosis. Advanced stage, age, focal weakness, cranial nerve palsies, presence of any infarction other than a purely hemispheric infarction, and hydrocephalus are predictors of mortality at 3 months.

CNS tuberculoma is a benign condition with a good prognosis and effective therapy options. TB of the spine may evolve into paraplegia, spinal tumor syndrome, and kyphosis. Early diagnosis and prompt treatment can reverse paralysis and minimize the potential disability resulting from Pott's paraplegia. When needed, a combination of conservative therapy and surgical decompression yields successful results in most patients with tuberculosis of the spine and who have neurological complications.

	Mortality (prognosis quoad vitam)	Residual disability (prognosis quoad valetudinem)
TBM	20–50 % [3, 4] HIV-negative 25 % HIV-positive 67 %	Frequency 20–50 % Hydrocephalus Cranial nerve palsies Ophthalmoplegia Seizures Psychiatric disorders Ataxia Hemiparesis Blindness Deafness Mental retardation [3, 4]

8.1.4 CNS Syphilis

Key Facts

- **Terminology and definitions** – *Treponema pallidum.*
- **Clinical features** – Primary, secondary, and tertiary syphilis.
- **Diagnosis**
  - **Blood** – treponemal and nontreponemal tests.
  - **CSF** – positive VDRL or RPR.
- **Prognosis**
  - **Principles of treatment** – Penicillin G.
  - **Disability** – HIV is a predisposing factor to CNS syphilis. Tertiary syphilis may complicate with dementia paralytica, general paresis, and tabes dorsalis.

Terminology and Definitions

The diagnosis of neurosyphilis requires a CSF WBC count of 20 cells/μL or greater, or a reactive CSF Venereal Disease Research Laboratory (VDRL) test result. The burden from neurosyphilis is unknown, because national reporting of the disease is incomplete. Resurgence of early syphilis contemporaneously with the global epidemic of AIDS has renewed interest in syphilis pathogenesis and the host response.

8.1.4.1 Clinical Features

Syphilis is classified as primary (presence of chancre at the inoculation site), secondary (hematogenous dissemination), and tertiary (tabes dorsalis and general paresis, cardiovascular syphilis). Neurosyphilis can occur at any time in the course of syphilis.

Involvement of VIII cranial nerve can result in otosyphilis. Ocular involvement can occur (chorioretinitis, neuroretinitis, retinal vasculitis, and retinal detachment).

8.1.4.2 Diagnosis

Blood – Treponemal (TPHA) and nontreponemal tests (VDRL, RPR).

CSF – Pleocytosis (45 WBC per high power field), low glucose (2/3 serum glucose), and elevated protein (445 mg/dL). Positive VDRL or RPR

8.1.4.3 Prognosis

Principles of Treatment

The treatment recommendations for patients with neurosyphilis or ocular syphilis is aqueous crystalline penicillin G at 18–24 million units per day, either by continuous infusion or in divided doses, for 10–14-days.

Mortality and Disability

Immunosuppression due to human immunodeficiency virus (HIV) infection supports the development of neurosyphilis with parenchymal affection, predominantly if peripheral blood CD4-cell counts are below 350 cells/uL. The incidence of relapses or reinfections of patients after treatment of an early syphilis is believed to be more likely in HIV patients. Early and effective treatment may not only prevent further disease progression, but may also allow for a complete recovery.

Tertiary neurosyphilis may result in severe sequelae such as dementia paralytica or general paresis and tabes dorsalis not responsive to antibiotic treatment. Bilateral hearing loss may complicate ocular syphilis. Visual loss is common after chorioretinitis [5].

8.1.5 CNS Lyme Disease

Key Facts

- **Terminology and definitions**: *Borrelia burgdorferi*.
- **Clinical features** – Meningitis, encephalomyelitis, cranial neuropathies.
- **Diagnostic markers**
  - **Blood** – Ab anti-Borrelia.
  - **CSF** – Ab anti-Borrelia.
- **Prognosis**
  - **Principles of treatment** – Cephalosporins.
  - **Disability** – Limb paresis, chronic infection.

8.1.5.1 Terminology and Definitions

Lyme borreliosis is the most common human tick-borne disease in the northern hemisphere. The responsible pathogen is *Borrelia burgdorferi* sensu lato.

The incidence of Lyme borreliosis varies considerably from region to region.

8.1.5.2 Clinical Features

Nervous system infection with *Borrelia burgdorferi* frequently causes meningitis and rarely causes encephalomyelitis. Altered cognitive function also can occur in the absence of central nervous system infection. Cranial neuropathies are probably the most widely recognized neurologic presentations of Lyme disease. Approximately 80 % of these involve the facial nerve, causing unilateral or bilateral facial paralysis.

8.1.5.3 Diagnostic Markers

Blood – *Borrelia burgdorferi*-specific IgM and/or IgG antibodies.

CSF – Lymphocytic pleocytosis, detection of intrathecally produced, *B. burgdorferi*-specific antibodies. PCR and culture (very low sensitivity).

8.1.5.4 Prognosis

Principles of Treatment

Parenteral treatment regimens with third generation cephalosporins for 10–14 days. There is also a growing body of evidence that oral regimens, particularly with doxycycline can be highly effective.

Mortality and Disability

The outcome after antibiotic treatment is generally good. The pain, typical for Bannwarth's syndrome, rapidly decreases under antibiotic therapy, and patients might be free of complaints even after one antibiotic dose. In the majority of cases, persisting objective symptoms after an adequate course of antibiotics are either due to irreversible damage (a limb paresis due to axonal loss) or might reflect a misdiagnosis in the majority of cases.

Because facial nerve palsy occurs frequently and is easily diagnosed, this group of patients has been the subject of several recent studies. If untreated, a significant number will develop persistent infection and late sequelae [6]. Some patients may develop a post-Lyme syndrome or chronic Lyme disease characterized by fatigue, malaise, and subjective perceptions of memory and cognitive impairment, but they usually have little compelling evidence of CNS infection or damage.

8.1.6 Infections of Ventriculoperitoneal Shunts

Key Facts

- **Terminology and definitions** – Bacterial or fungal infections of the shunt.
- **Clinical features** – Abdominal pain, fever (high in case of sepsis), meningeal signs, altered sensory and coma.
- **Diagnostic markers**
  - **Laboratory** – Overturf's diagnostic criteria for ventriculoperitoneal shunt infection.
    - **Blood** – Positive culture.
    - **CSF** – Positive culture.
- **Prognosis**
  - **Principles of treatment** – Medical + surgical treatment (*Staphylococcus aureus*).
  - **Disability** – Fulminant in head trauma and post-neurosurgical states. Increasing methicillin-resistant *S. aureus* (*MRSA*).

8.1.6.1 Terminology and Definitions

Ventriculoperitoneal shunting is a surgical procedure to treat excess cerebrospinal fluid (CSF) in the brain (hydrocephalus). Shunt surgery should be done as soon as hydrocephalus is diagnosed. Bacterial/fungal infection of the shunt, brain, or in the abdomen is one of the major risks of ventriculoperitoneal shunt placement (different studies report rates of CSF shunt infections ranging from 1.5 to 39 %).

8.1.6.2 Clinical Features

Infection from shunt may occur in case of a sepsis originating from other foci, or in case of abdominal infection causing peritonitis. Symptoms of infection manifest with abdominal pain, fever (high in case of sepsis), meningeal signs, altered sensory and coma.

8.1.6.3 Diagnostic Markers

Laboratory

Overturf's Diagnostic Criteria for Ventriculoperitoneal Shunt Infection: [7].

Definite shunt infection: Compatible clinical signs and symptoms + Isolation of bacterial pathogen from device puncture, lumbar puncture, or other significant site (overlying shunt wound, cellulitis, or shunt tubing).

Probable shunt infection: Compatible signs and symptoms; CSF consistent with bacterial infection; Negative blood, CSF, and device cultures for bacteria.

8.1.6.4 Prognosis

Principles of Treatment

Medical + surgical treatment: IV or intrathecal antibiotics or antimycotic treatment based on the isolated microorganism (in empirical treatment, think about *S. aureus*, skin bacteria (Candida), and Gram-negative intestinal bacteria). Shunt removal and externalized ventricular drainage must be considered, because surgical treatment seems to be more efficacious than medical treatment, with a higher rate of initial cure, and lower morbidity and mortality rates.

Mortality and Disability

Morbidity and mortality depend on the age of the patient, the type of microorganism involved, and the underlying conditions. Fulminant course and fatalities are observed usually among adults with head trauma and postneurosurgical states; in contrast, pediatric cases following premature delivery involve both a more indolent course and a more favorable outcome [8]. Increasing *MRSA* strains affect treatment and prognosis of these kinds of infections. Prognosis of infections caused by Gram-negative bacteria is considered particularly poor: they are difficult to suspect because patients often appear relatively well at presentation, and are usually of mixed infections.

8.1.7 CNS Involvement in Endocarditis

Key Facts

- **Terminology and definitions** – CNS complications of infective endocarditis.
- **Clinical features** – Embolic occlusion and/or stroke. Mycotic aneurism.
- **Diagnostic markers**
  - **Blood** – Positive culture.
  - **Echocardiography** – Findings of vegetating or ulcerative lesions suggestive for endocarditis.
  - **Cerebral CT scan** – Findings of vascular embolism.
- **Prognosis**
  - **Principles of treatment** – IV antibiotic, delayed surgery.
  - **Disability** – Mortality 58–74 %.

8.1.7.1 Terminology and Definitions

The incidence of central nervous system (CNS) complications in infective endocarditis is approximately 30 %, and these manifestations are often the first sign of illness (47 % of the time in one series).

8.1.7.2 Clinical Features

Approximately 15–50 % of the CNS manifestations of infective endocarditis are due to embolic occlusion and/or stroke. Aneurysms of arteries may occur in around 5–10 %. A leak of a mycotic aneurysm or an underlying focal lesion can produce meningeal irritation and cause secondary aseptic meningitis. The overall prevalence of hemorrhage in CNS involvement of infective endocarditis is 3–7 %.

8.1.7.3 Diagnostic Markers

Blood – Positive culture.

Echocardiography – Findings of vegetating or ulcerative lesions suggestive for endocarditis.

Cerebral CT scan – Findings of vascular embolism.

8.1.7.4 Prognosis

Principles of Treatment

Intravenous (IV) antibiotic treatment for 4–6 weeks (targeted on the isolated microorganism). Forty percent of patients with infective endocarditis will need cardiac surgery, primarily for valve repair or replacement. Timing of surgery in patients with infective endocarditis and embolic stroke remains controversial, but a report suggested that surgery can be performed relatively safely within 3 days of stroke, if heart failure is severe; otherwise, a delay of 2–4 weeks is preferable. In patients with associated hemorrhage, a delay of at least 4–6 weeks is preferred. Operative mortality is variable, but has been reported as 7.6 %. Anticoagulants are contraindicated because of the increased risk of CNS hemorrhage.

Mortality and Disability

Endocarditis can have profound and devastating neurological consequences [9]. In most cases, the neurological sequelae are present before the initiation of antimicrobial therapy (76 %). Studies have shown that the mortality of patients with bacterial endocarditis with CNS involvement is much greater (58–74 %) than that of patients who do not have CNS involvement (20–56 %). In one study, during the acute phase of infective endocarditis, 24 % of patients with neurological complications died, while only 10 % of those without neurological complications died. Among the patients with neurologic involvement, mortality was 25 % in those treated medically and 20 % in those treated surgically. In one series, 38 major embolic events occurred in 37 patients; 30 of these 37 patients died (81 % mortality).

8.2 CNS Fungal Infections

8.2.1 Aspergillus Species

Key Facts

- **Terminology and definitions** – *Aspergillus* species
- **Clinical features** – Cerebral abscesses, paranasal sinusitis, meningitis, meningoencephalitis, arachnoiditis, and ventriculitis. Mycotic aneurysms, cerebral infarcts, multifocal cerebritis.
- **Diagnostic markers**
  - **Lesion** – Biopsy.
  - **Blood** – *Aspergillus* species: Galactomannan.
  - **CSF** – Galactomannan.
- **Prognosis**
  - **Principles of treatment** – Voriconazole.
  - **Disability** – Mortality 50–80 %. Prognostic factor: immunosuppression.

8.2.1.1 Terminology and Definitions

The genus *Aspergillus* is an anamorphic member (asexual form) of the family Trichocomaceae. *Aspergillus species* are filamentous fungi spread worldwide, usually acquired by inhalation of *Aspergillus* conidia. CNS aspergillosis may result from: hematogenous dissemination, directed extension from the paranasal sinuses or eye, or direct inoculation. The most relevant risk factors for invasive aspergillosis include hematological disorders, prolonged and profound neutropenia (<100 neutrophils/ul), neoplastic diseases, solid organ transplantation, and allogenic hematopoietic stem cell transplantation. In this setting, the frequency of CNS infections ranges from 14 to 42 %.

8.2.1.2 Clinical Features

Cerebral abscesses, paranasal sinusitis, meningitis (usually associated with adjacent cerebral lesion), meningoencephalitis, arachnoiditis, and ventriculitis. Mycotic aneurysms, cerebral infarcts, multifocal cerebritis.

8.2.1.3 Diagnostic Markers

Lesion biopsy with direct examination and culture.

Blood – Culture rarely positive. Presence of galactomannan (a cell-wall polysaccharide released by *Aspergillus* during growth).

CSF – Culture is rarely positive. Inflammatory findings and hypoglycorrhachia. Presence of galactomannan in CSF.

8.2.1.4 Prognosis

Principles of Treatment

First choice: voriconazole. Second line therapy: itraconazole, posaconazole, liposomal amphotericin B. Therapeutic drug monitoring of voriconazole is needed to reduce drug toxicity. Radical surgical debridement for *Aspergillus* brain abscess.

Mortality and Disability

	Global case fatality rates (CFR)	Immunocompetent CFR	Immunocompromised CFR
Brain abscess	50–70 %	–	–
Meningitis [10]	72.1 %	63.5 %	83 %
CNS/invasive aspergillosis [11]	–	–	88.1 %

Immunosuppression and disseminated infection are risk factors of mortality. Outcomes of CNS aspergillosis appear to be improving after extensive use of voriconazole; complete and partial responses occurring in 35 % of patients, and 31 % surviving for a median observation time of 390 days. In case with space-occupying lesions, neurosurgical intervention is associated with improved survival. A CFR of 88.1 % is reported for disseminated and cerebral aspergillosis [11].

8.2.2 Candida Species

Key Facts

- **Terminology and definitions** – *Candida* species.
- **Clinical features** – Chronic meningitis, cerebritis, disseminated disease.
- **Diagnostic markers**
  - **Blood** – Positive culture, Beta-D-glucan, mannan/antimannan.
  - **CSF** – positive culture, mannan.
  - **Imaging** – Microabscesses.
- **Prognosis**
  - **Principles of treatment** – Liposomal Ampho B, fluconazole.
  - **Disability**: Mortality in ELBW = 30 %; 10–30 %, in general population.

8.2.2.1 Terminology and Definitions

Candida species are yeasts. *C. albicans* is the most common species responsible for candidal brain abscess (90 %). The organism is a normal commensal of humans. Usually, CNS candidiasis results from hematogenous dissemination, but *Candida* meningitis may result from infection from a ventricular shunt. Risk factors for neurocandidiasis are broad-spectrum antibiotic therapy, prematurity, parenteral nutrition, malignancy, treatment with corticosteroids, transplantation, indwelling devices, abdominal surgery, diabetes, dialysis, multiple sites colonization, and parenteral drug abuse.

8.2.2.2 Clinical Features

Chronic meningitis, diffuse cerebritis with multiple microabscesses (<3 mm), mycotic aneurysms: subarachnoid hemorrage and/or subdural empyema can appear. Approximately 50 % of patients with *Candida* meningitis have disseminated disease in other organs.

8.2.2.3 Diagnostic Markers

Blood – Culture: positive in 50–60 % of cases of disseminated infection. Beta-D-glucan (a cell-wall component): high negative predictive value. Mannan antigen/antimannan antibody test.

CSF – Culture: positive in 50 % of cases. Inflammatory findings with hypoglycorrhachia and lymphocyte pleocytosis. Positive CSF mannan.

MRI/TC – Microabscesses in the joint between the gray and white matters; basal ganglia and the cerebellum.

8.2.2.4 Prognosis

Principles of Treatment

Liposomal amphotericin B with or without flucytosine is recommended for several initial weeks of treatment. Fluconazole is recommended as a step-down therapy. Removal of all infected devices is mandatory.

Mortality and Disability

CNS candidiasis	Mortality	Disability
ELBW[a] infants	29.6 % [12]	>50 %
General population	10–30 % [13]	18–29 % [13]

[a]Extremely low birth weight infants

Prognostic factors associated with a poor prognosis are (1) the delay to initiate antifungal therapy (more than 2 weeks after start of symptoms); (2) glycorrhachia<35 mg/100 mL, (3) development of intracranial hypertension and focal neurological deficits.

Extremely low birth weight infants (ELBW, birth weight <1000 g): death or neurodevelopmental impairment is observed for 73 % of ELBW infants who developed candidiasis [12]. Neurodevelopmental impairment occurs in nearly 53 % of children with *Candida* meningitis; also, cerebral palsy and blindness can occur (13.3 % and 6.7 % of patients, respectively). Vision impairment is observed in 46.7 % of patients. Also, hydrocephalus can develop.

General population Mortality by *Candida* meningitis varies between 10 % and 30 % and is generally correlated with the degree of immunosuppression and the underlying disease.

8.2.3 *Cryptococcus neoformans* and *C. gattii*

Key Facts

- **Terminology and definitions** – *Cryptococcus neoformans* and *C. gattii*.
- **Clinical features** – Cryptococcal meningitis (CM), meningoencephalitis, cryptococcoma.
- **Diagnostic markers**
  - **Blood** – Culture, antigen detection.
  - **CSF** – Culture, India ink staining, antigen detection.
- **Prognosis**
  - **Principles of treatment** – Antifungal drugs.
  - **Disability** – Mortality rate from 25 to 30 %, neurologic sequelae in 40 % of patients.

8.2.3.1 Terminology and Definitions

Cryptococcus is an encapsulated yeast. Two species are human pathogens: *C. neoformans* is the most common and is found in most temperate regions (in soil contaminated with avian excreta), *C. gattii* has been related to a recent outbreak in humans. Approximately one million cases of cryptococcal meningitis occur throughout the world each year; the global incidence among HIV/AIDS patients ranges from 0.04 to 12 % per year. *C. neoformans* infection has been documented in 2.8 % of organ transplant recipients.

In immunocompromised host, the fungus can spread from the lung (site of primary infection) to the CNS. Conditions associated with deficit of T cell-mediated immunity and humoral immunity can predispose to develop symptomatic CNS cryptococcosis: advanced HIV infection, prolonged treatment with corticosteroids, organ transplantation and immunosuppressive therapy, malignancy, diabetes.

8.2.3.2 Clinical Features

Cryptococcal meningitis (CM), meningoencephalitis (usually subacute or chronic clinical course). Sometimes, space-occupying lesions (cryptococcoma) can develop.

8.2.3.3 Diagnostic Markers

Blood – Culture: positive in 47–70 % of HIV-infected patients, 21 % of HIV-uninfected patients. Detection of cryptococcal polysaccharide antigen: more than 90 % sensitive and specific for *C. neoformans*.

CSF – Culture: positive in 75 % of patients. Microscopic examination: India ink staining. Very low or normal CSF leukocyte counts, elevated protein concentration, hypoglycorrhachia. Detection of cryptococcal polysaccharide antigen.

8.2.3.4 Prognosis

Principles of Treatment

In HIV-infected patients and transplant recipients: amphotericin B deoxycholate or liposomal plus flucytosine followed by fluconazole. In patients with true hydrocephalus or elevated intracranial pressure, refractory VP shunts should be placed.

In HIV patients, both treatments for *Cryptococcus* and HIV must be started concomitantly.

Mortality and Disability

	Mortality	Disability
CM Pregnant women	25 %	–
CM Immunocompromised	In general, 25–30 % *HIV-positive patients*: 10 week case fatality rates—9 % in Western contries, 70 % in sub-Saharan Africa [14] *Organ transplant recipients*: 49 % [15]	In general, 40 % *Neurologic sequelae*: visual loss or visual field defect and diplopia. Mental impairment; hydrocephalus and cranial nerve palsies (most frequent in case of *C. gattii* infection) 20–25 %: relapse
Cryptococcoma	50 %	>50 %: neurologic deficit (high-risk patients, if concurrent meningitis and age >40 years)

If untreated, CM is a fatal disease. The most important prognostic factor remains severity of the underlying disease. Furthermore, there are different major prognostic factors associated with a poor prognosis:

(a) High burden of organism in CSF at presentation and/or high CSF or serum cryptococcal antigen titers (1:32 or more)
(b) CSF leukocyte concentration < 20 cells/mm^3,
(c) CSF glucose < 40 mg/dL before treatment

(d) Elevated intracranial pressure (250 mm H2O or more)
(e) Corticosteroid therapy (>20 mg prednisolone daily)
(f) Lymphoreticular malignancy
(g) Abnormal mental status at presentation and
(h) Disseminated disease

Cerebral infarcts during CM are associated with a 100 % mortality rate. Lack of significant decrease in CSF and serum antigen titers during treatment, a CSF/serum cryptococcal antigen titers of 1:8 or more at the end of treatment, and glycorrhachia persistently abnormal after 4 weeks of treatment are associated with the risk of relapse.

CM in AIDS patients The introduction of antiretroviral therapy has produced marked increase of survival of patients with cryptococcal meningitis. In patients with AIDS, low serum albumin concentration, wasting syndrome (low body mass index), and low CD4 cell count (<50 cells/mL) are associated with treatment failure.

CM in organ transplant recipients Abnormal mental status, absence of headache, and preexistent renal failure (serum creatinine >1.5 mg/dL on admission) correlated with poor outcome in patients with CNS cryptococcal infection [15].

8.2.4 Cerebral and Rhinocerebral Mucormycosis

Key Facts	
• **Terminology and definitions**: Rhinocerebral mucormycosis. • **Clinical features** – Cavernous sinus thrombosis, neurologic deficits, epidural and subdural abscesses. • **Diagnostic markers** – **Blood** – Culture usually negative. – **CSF** – Culture usually negative.	• **Prognosis** – **Principles of treatment** – Liposomal amphotericin B in association with surgical resection. – **Disability** – Mortality rate from 50 to 70 %, facial deformities after surgical debridement, permanent blindness can develop.

8.2.4.1 Terminology and Definitions

The most frequent agent of mucormycosis is *Rhizopus* species (47 %), followed by *Mucor* species (18 %). These filamentous fungi are found worldwide in decaying organic matter. In the USA, an annual incidence of 1.7 cases per million people is estimated; cerebral involvement is reported in about 30 % of cases. The most frequent route of infection is via inhalation. Specific risk factors for invasive mucormycosis are: metabolic acidosis in poorly controlled diabetes mellitus, primitive or iatrogenic immunodepression, iron overload conditions and therapy with deferoxamine, trauma, burns, head surgery, or intravenous drug use.

8.2.4.2 Clinical Features

Rhinocerebral mucormycosis: cavernous sinus thrombosis may develop. Focal neurologic deficits may appear when septic emboli from the carotid artery occur. Intracranial complications include epidural and subdural abscesses.

8.2.4.3 Diagnostic Markers

Blood – Culture: usually negative

CSF – Culture: usually sterile; inflammatory findings

CT – Mucosal thickening, pansinusitis, air–fluid levels, bony erosion. Severe infection can involve brain or orbits.

8.2.4.4 Prognosis

Principles of Treatment

First-line treatment: Liposomal amphotericin B in association with correction of underlying metabolic abnormalities. Posaconazole can be used in case of high risk for relapsing infection. Radical surgical resection is mandatory to avoid the spread of infection.

Mortality and Disability

The most important predictors of outcome are as follows:

1. Underlying disease (active hematologic malignancy and allogeneic hematopoietic stem cell transplantation are associated with poor outcome)
2. Extent of the local infection (in particular, patients with carotid artery and/or cavernous sinus involvement are at high risk for death)
3. Delay in the diagnosis and treatment

Hemiparesis, bilateral sinus and orbital involvement, facial necrosis, renal impairment, and treatment with deferoxamine are associated with poor survival. With the introduction of amphotericin B and aggressive surgical treatment, the mortality rate associated with rhinocerebral disease ranges from 50 to 70 %.

In a review of 929 cases of zygomycosis, rhinocerebral infections and localized cerebral infections are associated with a mortality of 62 %; in patients with cerebral disseminated disease, mortality is 98 % [16].

Mortality among diabetic patients with rhinocerebral form seems to be lower than patients that present other causes of immunosuppression. Rhinocerebral mucormycosis can be a devastating fungal infection; survivors may present facial deformities following surgical debridement or maxillectomy. Central retinal artery occlusion or optic nerve infarction/necrosis can cause permanent blindness.

8.2.5 Dimorphic Yeasts (*Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*)

Key Facts
• **Terminology and definitions** – Dimorphic yeasts. • **Clinical features** – Subacute or chronic meningoencephalitis, spinal granuloma, intracranial abscess. • **Diagnostic markers** – **Blood** – Serology, PCR, culture, antigen detection. – **CSF** – Culture, antigen detection. • **Prognosis** – **Principles of treatment** – Antifungal drugs. – **Disability** – High mortality in immunocompromised patients, high risk of relapse.

8.2.5.1 Terminology and Definitions

Dimorphic yeasts are endemic on the American continent. In people coming from endemic areas, clinicians have to consider this kind of infection also. Immunocompetent patients can be infected, but disseminated disease more commonly occurs in immunocompromised hosts. CNS involvement is reported from 5 to 50 % of cases of disseminated disease.

8.2.5.2 Clinical Features

All these dimorphic yeasts can cause subacute or chronic meningoencephalitis, epidural or spinal granuloma, intracranial abscess.

8.2.5.3 Diagnostic Markers

Blood – *B. dermatitidis*, *C. immitis*, *P. brasiliensis*, *H. capsulatum*: Serological tests.

- *C. immitis*: *Coccidioides* Polymerase chain reaction.
- *H. capsulatum*: Culture: positive in up to 50 %.
- *P. brasiliensis*, *H. capsulatum*: Antigen detection.

CSF – *B. dermatitidis*: Culture: rarely positive; *C. immitis*: culture positive in 25–35 % of cases, *H. capsulatum*: Culture positive in 25–65 % of patients
- *B. dermatididis*, *H. capsulatum*: Antigen detection.
- *C. immitis*, *H. capsulatum*: Serological tests
- *C. immitis*: CSF eosinophilia, inflammatory findings, and hypoglycorrhachia.
- *H. capsulatum*: Hypoglycorrhachia and elevated protein, cell counts range from 10 to 100/μL (mostly lymphocytes).

8.2.5.4 Prognosis

Principles of Treatment

- *B. dermatitidis*. The first-line treatment is liposomal amphotericin B, followed by an oral azole and surgical management of mass lesions.
- *C. immitis*. Fluconazole as initial therapy; drainage or resection of mass lesions. If hydrocephalus develops, shunting procedure is required.
- *H. capsulatum*. Liposomal amphotericin B, followed by itraconazole.
- *P. brasiliensis*. Sulfonamide; in case of severe disease, amphotericin B.

Mortality and Disability

CNS disease	Mortality	Disability
B. dermatitidis	–	Ocular disease [17]
C. immitis	20–40 %	Hydrocephalus (20–50 %) [18] CNS vasculitis (40 %) [18]
H. capsulatum	–	–
P. brasiliensis	–	–

- *Blastomycosis*: Mortality rate is 0–2 % among immunocompetent patients and 30–40 % among immunocompromised. Ocular disease is a rare but sight-threatening complication of CNS blastomycosis [17].
- *Coccidioidomycosis*: Factors associated with poor outcome are hydrocephalus (12-fold increased risk of mortality [18]), underlying disease, nonwhite race. Low or absent CSF antibody titer is considered a good prognostic factor. Complications resulting from stroke may occur in 10–40 % of patients, with mortality ranging from 15 to 70 %. Because of the high frequency of relapse of CNS disease (50 % of subjects after initial treatment), patients should remain on suppressive therapy indefinitely.
- *Histoplasmosis*: Cure rate in meningitis is 50 %, with a high risk of relapse.
- *Paracoccidioidomycosis*: There is no data about mortality of CNS disease.

8.3 CNS Parasitic Infections

8.3.1 Cerebral Malaria (CM)

Key Facts

- **Terminology and definitions** – Cerebral malaria.
- **Clinical features** – Dysconjugate gaze, symmetric upper motor neuron lesion, increased intracranial pressure, coma.
- **Diagnostic markers**
  - **Blood** – Thick smears and thin smears, rapid diagnostic test, PCR.
  - **CSF** – Increase of protein, lymphocytosis.
- **Prognosis**
  - **Principles of treatment** – Artemisinin derivatives.
  - **Disability** – Mortality about 20 % in general population, residual disability in 11 % of children.

8.3.1.1 Terminology and Definitions

CM is almost exclusively caused by *Plasmodium falciparum*; only in few cases, it is caused by *P. vivax* and *P. malariae*.

8.3.1.2 Epidemiology

Mosquitoes of the genus *Anopheles* transmit Malaria person to person. There were 216 million episodes of malaria in 2010, of which 81 % were in the African Region, about 91 % being due to *P. falciparum. P. falciparum* is confined to tropical and subtropical regions. The incidence of cerebral malaria in malaria-endemic areas of sub-Saharan Africa is 1–12 cases per/1000 children per year.

8.3.1.3 Clinical Features

Dysconjugate gaze, symmetric upper motor neuron lesion, manifestations of increased intracranial pressure, and coma. Coma is estimated through Glasgow coma scale (unarousable coma GCS ≤7) (see Chap. 4). In young children who have not yet learned to speak, Blantyre coma scale (BCS, unarousable coma<=2) is employed.

8.3.1.4 Diagnostic Markers

The classic histopathological finding of fatal CM is the intense sequestration of parasitized erythrocytes in the cerebral microvasculature.

The three proposed criteria for the diagnosis of cerebral malaria: (1) unarousable coma, (2) exclusion of other encephalopathies, and (3) confirmation of Plasmodium infection.

Blood – Microscopy: *Thick smears* and *thin smears* are used to determine the *Plasmodium* species. Rapid diagnostic test: specificity 99 % and sensibility 96 %, but does not replace microscopy. Molecular diagnosis: PCR.

CSF – Mildly increased protein and lymphocytes.

8.3.1.5 Prognosis

Mortality and Disability

	Children	Adults
Mortality	18.6 % (75 % within 24 h of admission)	20 %; about 50 % occur within 24 h
Residual disability	11 % Transient ataxia (2.5 %) Hemiparesis (4.4 %) Quadriparesis (3.5 %) Hearing (1.9 %), visual (2.3 %), speech impairment (2.1 %) Behavioral difficulties (1.3 %) Epilepsy Memory, attention, and executive functions impairment Psychiatric disorders	<5 % Isolated cranial nerve palsies Mononeuritis multiplex Polyneuropathy Extrapyramidal tremor Other cerebellar signs, psychiatric symptoms

Most patients with CM seem to make a full recovery, but neurocognitive sequelae have been increasingly recognized. Most deaths happen within 24 h of admission and are suggestive of transtentorial herniation or cardiorespiratory arrest in association with severe metabolic acidosis. Mortality is higher among children <3 years.

Cold periphery, secondary to respiratory distress or circulatory failure, a deep coma (GSC ≤ 7 or BCS ≤ 2), generalized hyporeflexia, protracted convulsions or a biphasic clinical course characterized by recovery of consciousness followed by recurrent convulsions, and coma are the strongest clinical predictors of death and neurological sequelae [19, 20]. Laboratory findings of prognostic significance are prolonged hypoglycemia or multiple episodes of hypoglycemia, acidosis, parasites density ≥ 500,000/μL, elevated plasma or CSF lactate, leukocytosis, severe anemia, low platelet levels, and elevated urea levels on admission [19, 20].

Principles of Treatment

Antimalarial drugs: Artemisinin derivatives are first-line drugs, in particular, parenteral artesunate or quinine in alternative with a leading dose.

8.3.2 Neurotoxoplasmosis

Key Facts
• **Terminology and definitions** – Neurotoxoplasmosis, congenital toxoplasmosis. • **Clinical features** – Toxoplasmic retinochoroiditis (immunocompetent), multiple focal lesions (immunocompromised); intracranial calcifications, hydrocephalus, and chorioretinitis (congenital toxoplasmosis). • **Diagnostic markers** – **Blood** – Serology, Western Blot, PCR. – **CSF** – PCR – **Imaging** – Focal rounded lesions with ring enhancement. • **Prognosis** – **Principles of treatment** – Pyrimethamine/sulfadiazine, spiramycin. – **Disability** – Hydrocephalus, permanent focal motor and sensory deficits, or seizures (16 % of immunocompromised); chorioretinitis, intercranial calcification, hydrocephalus (10–30 % of newborns).

8.3.2.1 Terminology and Definitions

Toxoplasma gondii, obligate intracellular coccidian pathogen, family of Sarcocystidae.

8.3.2.2 Epidemiology

About 25–30 % of the world's human population is infected by *Toxoplasma*. Encephalitis is the most common and often fatal manifestation of Toxoplasmosis in immune-compromised hosts with T cell, especially in AIDS patients (CD4 + <200 cell/μL), and it is due to reactivation of latent infection. Incidence of Toxoplasma encephalitis (TE) decreased by half after introduction of HAART. Congenital toxoplasmosis (CT) commonly involves CNS.

The incidence of symptomatic CT ranges from 0.34 (UK) to 9 (Brazil) per 10,000 live births. Transmission of *T. gondii* to humans occurs commonly by eating undercooked infected meats or by inadvertent ingestion of oocysts from cat feces (contamination of water, soils, vegetables, and fruits).

8.3.2.3 Clinical Features

Immunocompetent host: TE is uncommon. Acute toxoplasmic retinochoroiditis may precede or accompany the CNS process. Immunocompromised host: Usually characterized by multiple focal lesions. The most common presentation (75 % of cases) is the subacute onset of focal neurologic abnormalities. Spinal cord involvement can occur. Classical triad of CT includes intracranial calcifications, hydrocephalus, and chorioretinitis.

8.3.2.4 Diagnostic Markers

Blood IgA, IgM, IgG, avidity of IgG, Western blot of IgG and IgM, and parasite detection by PCR.

CSF Mild pleocitosis, elevated protein, normal glucose. DNA detection by PCR.

Brain biopsy Vascular proliferation, perivascular inflammatory infiltrate, necrosis with possible toxoplasmic tachyzoites. Immunohistochemistry identifies tachyzoites.

MRI/TC – Multiple focal rounded lesions with ring enhancement, prevalent in corticomedullary junction (Fig. 8.2).

8.3.2.5 Prognosis

Principles of Treatment

Treatment for toxoplasmosis is considered almost only in immunocompromised patients, in pregnant women to prevent the transmission to fetus, and in children with congenital disease. Immunocompromised patients: The treatment of choice is represented by the combination of

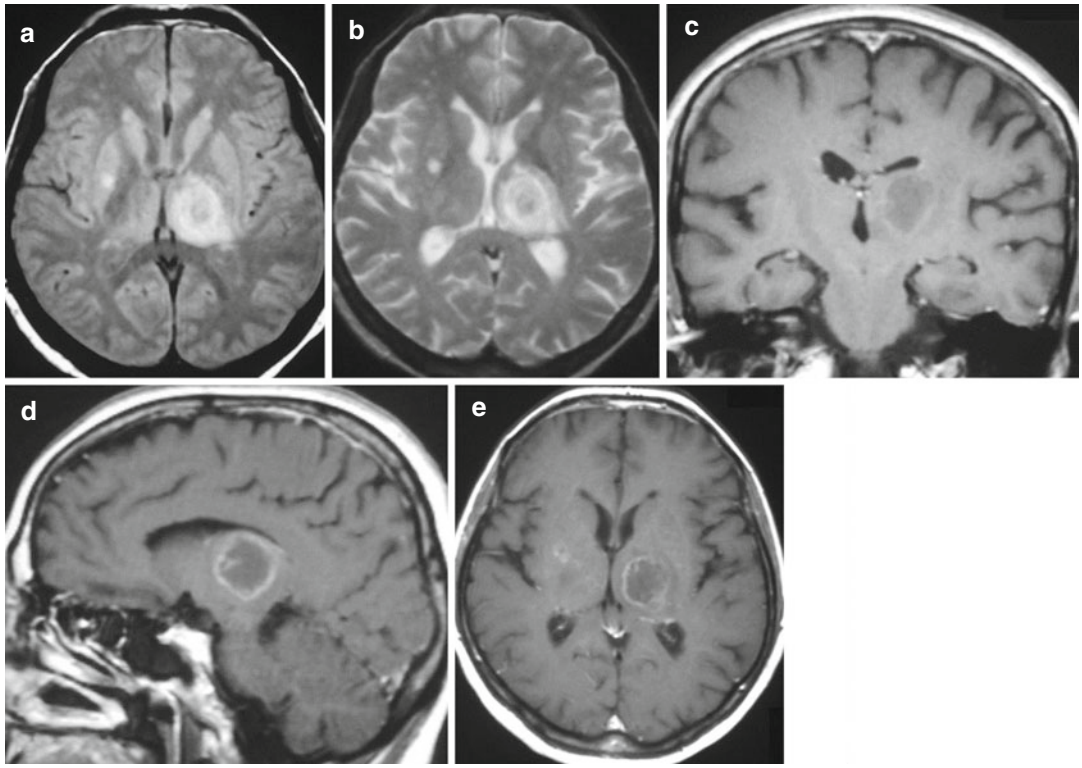

Fig. 8.2 Toxoplasmosis. Axial T2-weighted images (**a**, **b**), coronal T1-weighted image (**c**), and sagittal and coronal T1-weighted images after contrast medium administration (**d**, **e**) show a large oval image in the left thalamus and a small similar image in the right putamen. The oval image is characterized by a target pattern, and after contrast medium administration has a peripheral enhancement

pyrimethamine/sulfadiazine and folinic acid for 4–6 weeks. In AIDS patients, starting antiretroviral treatment (HAART) for HIV therapy is mandatory. Immunocompromised patients at risk of reactivation of toxoplasmosis require prophylactic treatment with trimethoprim/sulfamethoxazole. Pregnant women: Spiramycin is the treatment of choice. Treatment of congenital infection requires pyrimethamine/sulfadiazine.

Mortality and Disability

	Mortality	Residual disability
HIV on HAART	16 %[21]	Cognitive impairment, especially memory impairment Hydrocephalus, permanent focal motor and sensory deficits, or seizures [22] Alexia
Newborn	–	10–30 % 13 % chorioretinitis, 11 % intercranial calcification, 2 % hydrocephalus, and 3 % CNS abnormalities. Sequelae such as visual impairment, hearing problems, mental and cognitive abnormalities, epilepsy, palsies, and developmental delays may not become apparent for years.

Among AIDS population, patients who experienced HAART have a 50 % reduction in risk of developing TE, independently of HIV RNA load and CD4+ cell count. The efficacy of primary prophylaxis with trimethoprim/sulfamethoxazole in preventing TE is well-known.

Female sex, severe immunodeficiency, and absence of primary TE prophylaxis significantly

increase the risk of TE. However, HAART remains the main prognostic determinant in patients with advanced disease and severe immunodeficiency.

TE-specific mortality has a relevant role in negatively affecting survival, accounting for more than two-thirds of all deaths of AIDS patients. However, early starting of HAART after TE diagnosis (first 2 months after diagnosis) is associated with a strong reduction of the risk of clinical progression of disease and death [21]. Advanced age, altered mental status (GCS ≤8), and cognitive impairment are independent factors associated with an increased mortality and residual disabilities in AIDS patients with TE.

For patients having undergone heart and liver transplantations, prophylactic treatment with trimethoprim–sulfamethoxazole reduces the risk of infection by *T. gondii*.

8.3.3 American Trypanosomiasis (Chagas Disease)

Key Facts

- **Terminology and definitions** – American Trypanosomiasis (Chagas Disease).
- **Clinical features** – Acute phase: meningoencephalitis; chronic symptomatic Chagas disease: denervation of hollow viscera. Thromboembolism and stroke secondary to cardiopathy.
- **Diagnostic markers**
  - **Blood** – Identification of the parasite, serology, PCR.
  - **CSF** – Parasitic identification.
- **Prognosis**
  - **Principles of treatment** – Nifurtimox, Benznidazole.
  - **Disability** – Chronic infection: cognitive impairment, embolic stroke (22.6 %), and lesions of autonomous nervous system (25–30 %).

8.3.3.1 Terminology and Definitions

Trypanosoma cruzi is a single-celled protozoan parasite, causing Chagas disease. Occurrence of meningoencephalitis is rare during the acute phase of Chagas disease; sometimes, cerebral reactivation of chronic *T. cruzi* infection in immunosuppressed patients is possible.

8.3.3.2 Epidemiology

Chagas disease usually occurs in Latin America, where *T. cruzi* are mostly transmitted by the infected feces of blood-sucking triatomine bugs. Less frequently, it is due to infection through blood transfusion, vertical transmission, or organ donation. In the HIV-infected host, Chagas disease most often reactivates in the CNS, usually when the patient's CD4+ cell count is <200 cells/mm^3. Meningoencephalitis is the most common CNS manifestation of chronic infection in immunocompetent hosts. In the immunosuppressed hosts, CNS manifestations occur more frequently and can include meningoencephalitis or a brain mass.

8.3.3.3 Clinical Features

In the *acute phase*, meningoencephalitis is an uncommon cause of death. In the vast majority of persons with acute Chagas disease, the manifestations resolve spontaneously within 3–8 weeks.

In chronic symptomatic Chagas disease, 10–30 % of persons develop clinical manifestations of the disease. Chronic *T. cruzi* infection typically results from denervation of hollow viscera and consequent dysfunction. Thromboembolism, secondary to cardiopathy related to Chagas disease, can result in stroke.

8.3.3.4 Diagnostic Markers

Blood – Identification of the parasite through direct and indirect methods (xenodiagnosis, hemoculture). Serological tests and research of the parasite DNA by PCR.

CSF – Parasitic identification.

MRI/TC – Lesions involving both gray and white matter are ring-enhancing.

8.3.3.5 Prognosis

Principles of Treatment

Acute disease There are only two drugs available. Nifurtimox reaches parasitologic cure in about 70 % of patients; it causes severe side effects. Benznidazole has similar efficacy.

Chronic symptomatic infection Persons who have already developed cardiac or gastrointestinal symptoms should not be given antiparasitic treatment. Adults younger than 50 years with long-standing indeterminate *T. cruzi* infection should be treated. In patients older than 50 years, treatment is optional.

Mortality and Disability

	Mortality	Residual disability
Acute infection	<5 %	Chronic disease, 20–30 % of cases
Chronic infection		Cerebral and cerebellar atrophy Cognitive impairment Embolic stroke, 22.6 % Lesions of autonomous nervous system, 25–30 %

During the acute phase, the prognosis for Chagas disease depends on the patient's age and on the intensity and location of the lesions (table). In general, the acute phase is very severe among children younger than 2 years old, and is almost always fatal among those with myocarditis, heart failure, and meningoencephalitis. The prognosis may also be very poor in cases of the congenital form, thereby leading not only to abortion and prematurity but also to organic lesions in the liver, spleen, heart, and central nervous system, with neurological sequelae and mental deficiency. Many cases may be asymptomatic and remain in the indeterminate form. In the chronic cardiac form, the prognosis varies considerably. The presence of polymorphic ventricular extrasystoles or high-degree left-branch block constitutes the most important independent factor for poor prognosis [23]. The prognosis for the digestive and indeterminate forms is generally good, but with complications (esophageal cancer, obstruction with torsion, and necrosis of the colon). In different studies, the most compromised neurological functions are orientation and attention. In a large cohort of 1449 elderly people evaluated for cognitive impairment with the Mini-Mental State Examination, the authors found a graded and independent association between *T. cruzi* infection and the score in the test. The cognitive impairment may be associated to chagasic cardiomyopathy, treatment for cardiomyopathy, and/or direct central nervous system involvement [24]. In AIDS patients, good recovery may happen if early diagnosis is made and if trypanocidal therapy is initiated soon. In these cases, antiretroviral therapy is crucial to improve immunity. Trypanocidal therapy should be continued until CD4+ T-lymphocyte count is consistently above 200 cell/μL and persistent HIV suppression is confirmed. In elderly patients, an elevated B-type natriuretic peptide level, which is a good biomarker to predict cardiovascular events, was a strong and independent predictor of stroke mortality among *T. cruzi*–infected people. Atrial fibrillation was also associated with increased stroke mortality in this group [24]. Left ventricle systolic dysfunction, left ventricle ejection fraction below 35 %, and enlarged left atrial volume are independent risk factors for cerebrovascular events [24].

8.3.4 Human African Trypanosomiasis (HAT)

Key Facts

- **Terminology and definitions** – Human African trypanosomiasis (HAT).
- **Clinical features** – Headaches, daytime somnolence, nighttime insomnia, behavioral changes.
- **Diagnostic markers**
  - **Blood** – Buffy coat, stain with Giemsa, serological test, PCR.
  - **CSF** – Trypanosomes, WBC > 5 cells/μL, IgM (late stage).
  - **CT** *scan*
- **Prognosis**
  - **Principles of treatment** – *T. b. rhodesiense* HAT: melarsoprol; *T.b. gambiense*, HAT: nifurtimox–eflornithine.
  - **Disability** – Always fatal if untreated.

8.3.4.1 Terminology and Definitions

There are two subspecies of *T. brucei*: *rhodiense* in East Africa and *gambiense* in West Africa. *T. b. gambiense* accounts for more than 98 % of reported cases of sleeping sickness. The reservoir host for *T. b. gambiense* is man, while that for *T. b. rhodesiense* is wild game.

8.3.4.2 Epidemiology

In the last 10 years, over 70 % of reported cases occurred in the Democratic Republic of Congo (DRC), where HAT was considered the first or second greatest cause of mortality. The estimated number of cases is currently between 50,000 and 70,000/year.

8.3.4.3 Clinical Features

There are two clinical stages of the disease: stage 1, without involvement of CNS, and stage 2 (late, or CNS, stage). Invasion of CNS usually results in meningoencephalitis and/or meningomyelitis. Usually, patients manifest persistent headache, daytime somnolence followed by nighttime insomnia, behavioral changes and weight loss, and seizures in children (rarely in adults).

8.3.4.4 Diagnostic Markers

Blood – Buffy coat, stain with Giemsa, serological test, PCR detection.

CSF – Trypanosomes in the CSF or a WBC more than 5 cells per μL, or both (WHO criteria). Late-stage diagnosis: CSF IgM concentrations. Molecular biology: Sensitivity (87.6–100 %) and specificity (55.6–82.9 %). Leukocyte counts >20 cells/μL in CSF and intrathecal IgM synthesis have been proposed as modified criteria for diagnosis of stage 2 HAT.

Bone marrow aspiration – Detection of trypanosomes.

CT scan – Edema with scattered petechial hemorrhages.

Polysomnography – Alterations of sleep structure in CNS-stage HAT.

8.3.4.5 Prognosis

Principles of Treatment

The only effective drug at present for treating late-stage *T. b. rhodesiense* HAT is the trivalent organic arsenical melarsoprol. Eflornithine is effective for late-stage *T. b. gambiense*. The nifurtimox–eflornithine combination therapy (NECT) is the standard first-line treatment for CNS-stage *T. b. gambiense* HAT.

Mortality and Disability

HAT is always fatal if untreated. The gradual withdrawal from environmental stimuli progresses into mutism and inanition (debilitation from lack of nourishment). Patients waste and succumb, often by developing secondary bacterial infections.

High relapse rates have been reported previously among patients treated with melarsoprol. A CSF white cell count of 10 cells/mm^3 as the threshold between stage 1 and 2 cases seems to be associated with a higher risk of relapse. The CSF leukocytes count at 6 months has a good prognostic value for final efficacy outcome. This indicator can rule out relapse at 6 months post-treatment with a good degree of confidence (0.93 negative predictive value), but its ability to identify true relapses is suboptimal. For decision-making on individual patients followed-up in the field, a two-step algorithm using cutoff values of 5 (at the diagnosis), 50 (at 6 months), 20 leukocytes/mL (at 12 months) in CSF has shown a good performance [25].

8.3.5 Free-Living and Parasitic Amebic Infections

Key Facts

- **Terminology and definitions** – Free-living and parasitic amebic infections.
- **Clinical features** – Primary amebic meningoencephalitis (PAM), granulomatous meningoencephalitis (GAE): encephalitis, cerebral abscess.
- **Diagnostic markers**
  - **Blood** – Antibodies (GAE).
  - **CSF** – Pleocytosis, increased protein level, culture, nested-PCR.
  - **Brain biopsy**
  - **MRI** – Enhancing leptomeninges, ring-enhancing lesions.
- **Prognosis**
  - **Principles of treatment** – Amphotericin B (PAM), no treatment (GAE).
  - **Disability** – Fatal in >95 % of cases.

	Primary amebic meningoencephalitis (PAM)	**Granulomatous meningoencephalitis (GAE)**
Terminology and definitions Epidemiology	*Naegleria fowleri*, isolated from freshwater lake, river water, and soil all over the world	*Acanthamoeba* spp. and *Balamuthia mandrillaris* present in water and soil all over the world
Clinical features	Invasion of the brain via olfactory nerve. Average incubation: 2–5 days. The first symptom is usually a change in taste or smell with rapid progression to coma and death	Hematogenous spread from cutaneous or pulmonary lesions or invasion via olfactory nerve Encephalitis and cerebral abscess
Laboratory diagnosis	*CSF*: pleocytosis, increased CSF protein level, normal or decreased CSF glucose Detection of *Naegleria* through wet preparations, culture of CSF, and nested PCR.	*Blood*: Antibodies *CSF*: Moderately elevated protein, low to normal glucose, and lymphocytosis Rarely pathogens have been isolated from the CSF *Brain biopsy*: It is the most reliable diagnostic approach
Imaging	Enhancing leptomeninges, cisterns (most prominent around olfactory bulbs)	Ring-enhancing lesions, gyriform-enhancing
Principles of treatment	Amphotericin B	There is no established treatment [27]
Mortality and disabilities	Prognosis is fatal in >95 % of cases; there have only been a total of 9 known cases where people have survived PAM, out of about 200 published cases in the literature. Long-term morbidity in survivors is usually low, with complete recovery reported in all survivors [26]	The most distressing aspect is that the high level of mortality is due to lack of awareness combined with the lack of effective drugs As mortality rate is more than 95 %, neurological disability is negligible [27]

8.3.6 Neurocysticercosis (NCC)

Key Facts	
• **Terminology and definitions** – Neurocysticercosis. • **Clinical features** – Seizures, manifestations of increased intracranial pressure. • **Diagnostic markers** – **Blood** – Antibodies – **CSF** – Antibodies – **Imaging** – Four stages (vesicular, colloidal, "granulonodular," final stage of calcification).	• **Prognosis** – **Principles of treatment** – Praziquantel and albendazole. – **Disability** – Mortality, 15 %; subarachnoid, intraventricular, spinal, and mixed forms carry worse prognoses than parenchymal cases.

8.3.6.1 Terminology and Definitions

NCC is the infection of CNS caused by larval forms of *Tenia*.

8.3.6.2 Epidemiology

It is the most common preventable cause of epilepsy in the developing world, with two million people having epilepsy caused by *T. solium* infection. NCC is transmitted by ingestion of contaminated food by *T. solium* eggs (man is the intermediary host).

8.3.6.3 Clinical Features

Cysticerci may be located in brain parenchyma, subarachnoid space, ventricular system, or spinal cord. The most common manifestations of NCC are seizures. Focal neurological abnormalities and manifestations of increased intracranial pressure may arise after many years when larvae elicit immune response, and they may be exacerbated by antihelminthic therapy.

8.3.6.4 Diagnostic Markers

Blood – Anticysticercal antibodies. This test may be false-negative in up to 50 % of patients with a single cerebral cyst or in those with calcifications alone. The test may be positive in patients exposed to the adult parasite without developing cysticercosis.

CSF – Anticysticercal antibodies.

Imaging – Four stages (Diagnostic criteria revised from Del Brutto) [28]:

1. Vesicular: smooth, thin-walled cyst, no edema
2. Colloidal: hyperdense cyst fluid with surrounding edema
3. "Granulonodular" (healing): mild edema
4. Final stage of calcification (healed): small, calcified nodules (Fig. 8.3)

8.3.6.5 Prognosis

Principles of Treatment

Therapy usually includes a combination of symptomatic and cysticidal drugs. Surgery also has a role in the management of some patients. Two potent cysticidal drugs (praziquantel, PZQ, and albendazole, ABZ) have drastically changed the prognosis of most patients with NCC. Cysticidal drug therapy determines a resolution of both colloidal and vesicular cysticerci, reducing the risk of seizure recurrence [28].

The use of steroids (dexamethasone) is recommended during treatment with antiparasitic drugs. The main indication of steroids in NCC is related to the most severe forms of the disease, especially arachnoiditis.

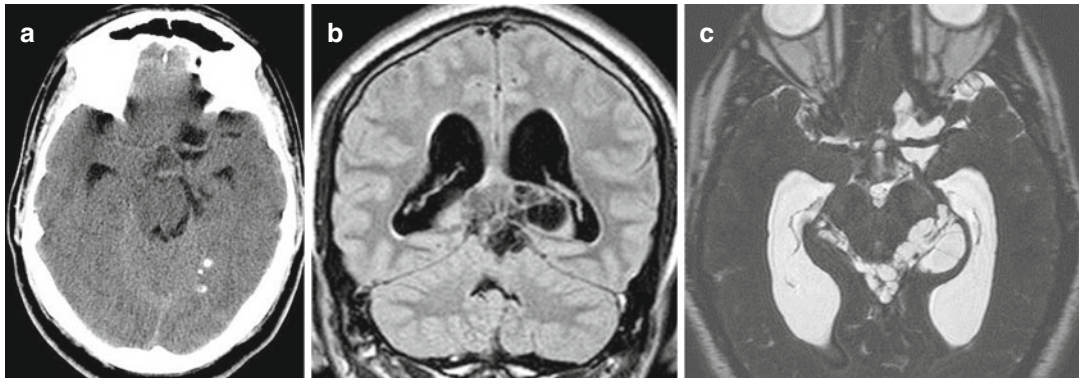

Fig. 8.3 Neurocysticercosis. CT scan (**a**) demonstrates calcified cyst in the left temporal–occipital region and enlargement of the temporal horns. Coronal FLAIR and Axial T2-weighted images (**b**, **c**) demonstrate symptomatic acute hydrocephalus and numerous thin-walled cystic lesions located in the perimesencephalic cisterns

Mortality and Disability

	Mortality	Residual disability
NCC (general)	15 %	Recurrent seizures Neurological deficits, hydrocephalus
Racemose and intraventricular form	>20 %	
Arachnoiditis	50 %	

Few data are available for the burden of mortality associated with NCC. Higher mortality is related to racemose and intraventricular forms (as shown in the table).

NCC can cause premature death. The prognosis for the most serious forms remain unsatisfactory. Benign parenchymal NCC has a relatively good prognosis with or without treatment (disappearance of cysts in 60–90 % of cases). Subarachnoid, intraventricular, spinal, and mixed forms carry worse prognoses than the parenchymal cases. Mortality rate in different forms of NCC is represented in the table above. Mortality most often results from severe intracranial hypertension associated with ventricular obstruction or adhesive ependymitis. Patients with hydrocephalus, large cysts, multiple lesions with edema, chronic meningitis, and vasculitis may not respond to treatment and have complications due to medical and surgical therapy. Prognostic factors associated with seizure recurrence include the development of parenchymal brain calcifications and the presence of both recurrent seizures and multiple brain cysts before the institution of therapy. In patients with single enhancing lesions (colloidal cysts), the development of brain calcification after therapy is also the main determinant for seizure relapse after withdrawal of antiepileptic drugs; in such cases, long-term antiepileptic treatment may be needed [28].

8.3.7 Schistosomiasis of CNS

8.3.7.1 Terminology and Definitions

Schistosomiasis is caused by different species of *Schistosoma*, depending on the region of the world. *S. mansoni* and *S. japonicum* cause intestinal disease, while *S. haematobium* is the agent causing urinary disease.

8.3.7.2 Epidemiology

Schistosomiasis is second only to malaria in human impact among tropical diseases and is the third most prevalent parasitic disease in the world. Schistosomiasis is prevalent in tropical and subtropical areas (90 % in Africa). Humans (definitive hosts) get infected through penetration of skin by motile cercariae present in freshwater. Intermediate host are snails. HIV may predispose to a disseminated miliary schistosomiasis.

Key Facts

- **Terminology and definitions** – Schistosomiasis of CNS.
- **Clinical features** – Acute schistosomal encephalopathy (ASE): transient headache and altered mental status. Pseudotumoral encephalic schistosomiasis (PES): tumor-like lesions. Spinal cord schistosomiasis (SCS): medullary, myeloradicular, and conus–cauda equina syndrome.
- **Diagnostic markers**
  - **Blood**: Eosinophilia, antibodies, PCR.
  - **CSF**: Lymphocytosis, elevated protein, antibodies.
  - **CT and MRI** scan to detect edema, granulomas, tumor-like lesions, intracerebral hematoma.
- **Prognosis**
  - **Principles of treatment** – Praziquantel, surgical extirpation in case of large granulomas.
  - **Disability** – ASE: symptoms resolve completely after early treatment. PES: possible cognitive impairment and refractory epilepsy. SCS: 65 % early-treated patients recover completely.

8.3.7.3 Clinical Features

Acute schistosomal encephalopathy (*ASE*): 1–5 %. Symptoms are transient and resolve within weeks. Headache and altered mental status occur in nearly all patients. Focal neurological deficits and seizures are usually transient. *Pseudotumoral encephalic schistosomiasis* (*PES*): 3–5 % of individuals infected with *S. japonicum*. The neurological manifestations are caused by tumor-like lesions. Seizures can occur.

Spinal cord schistosomiasis (*SCS*): More common in children and young adults living in endemic areas. It can cause medullary, myeloradicular, and conus–cauda equina syndrome [29].

8.3.7.4 Diagnostic Markers

Blood – Peripheral eosinophilia in ASE; Antibodies, antischistosoma; PCR.

CSF – Lymphocytosis, elevated protein, normal glucose. Eosinophils in about 50 %. Detection of antibodies to schistosomes by ELISA is specific.

CT and MRI scan of the brain Edema, granulomas, enhancing tumor-like lesions, intracerebral hematoma. Cerebellum is the most common site of PES. MRI of spinal cord for SCS: no specific findings.

Neurophysiology – EEG with epileptic anomalies.

Biopsy – Gives definitive diagnosis of SCS.

Stool and urine – Ova in stool or urine: positive in PES and in 50 % of cases of SCS.

Rectal biopsy – Histological findings of granulomatous disease, in particular in PES.

8.3.7.5 Prognosis

Principles of Treatment

Praziquantel (PZQ) is curative in 60–90 % of cases. Artemether (ART), unlike PZQ, kills immature migrating larvae, and it is synergistic with PZQ. When PZQ is ineffective, oxamniquine may be used for treatment. When large granulomas are present, surgical extirpation might be necessary. Anticonvulsants for seizures. In SCS, laminectomy is considered in patients with spinal compression [29].

Mortality and Disabilities

	Mortality	Residual disability
ASE	25 %	–
PES	–	Cognitive impairment Refractory epilepsy
SCS	11.5 %	Sensory and motor impairment

Spinal cord schistosomiasis carries a guarded prognosis. The outcome of ASE is usually good. Before the use of PZQ: 13 % full recovery, 74 % partial recovery, and 13 % poor recovery. Neurological symptoms resolve completely in most patients treated early with PZQ and steroids. PES has a good prognosis: most treated patients recover quickly and without any residual deficits. Possible neurological sequelae are cognitive impairment and refractory epilepsy. Cognitive abilities can affect malnourished children and those with heavy *S. haematobium* infections. School children who were infected with *S. japonicum* showed improved performance on working memory after treatment [29].

SCS has a variable outcome depending on both early treatment with high dose corticosteroids and PZQ and features of the diseases itself. Sixty-five percent of early-treated patients recover completely; other patients have sequelae from mild to severe. Medullary forms tend to be worse; cauda equina and myeloradicular forms have a better outcome [30].

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Leprosy

9

Meena Angamuthu Kanikannan

Key Facts

- **Definition**
  - Leprosy is primarily a disorder of the peripheral nerves due to chronic granulomatous infection by *Mycobacterium leprae.*
- **Clinical features**
  - Leprous neuropathy is a manifestation seen in all forms of leprosy.
  - Cutaneous sensory involvement with or without major nerve affection is the common presentation. Most diagnostically challenging form is the pure neuritic leprosy without dermatological manifestation.
  - Mononeuropathy mononeuritis multiplex (in nonlepromatous) and polyneuritis (in lepromatous form) are the patterns of neuropathy.
- **Diagnosis**
  - The three diagnostic cardinal features are: (1) anesthetic skin lesions, (2) thickened nerves, and (3) slit skin smears for acid-fast bacilli (AFB).
  - In pure neuritic leprosy (PNL) the gold standard for diagnosis is the histopathology which includes nerve skin and nasal mucosa biopsy.
  - **Imaging** – Localizes the nerve thickening and its extent of involvement evidentiates nerve abscesses, and allows to know the chronicity of the disease.
  - **HRUS** – Is the cheapest and technically convenient form of imaging.
  - **Genetics** – Several genes have been identified which may be involved the pathogenesis of the disease.
- **Top differential diagnosis**
  - Several disease states (hypertrophic and sensory neuropathies) can mimic various manifestations of leprosy and need to be considered in the differential diagnosis.
- **Treatment**
  - Educating the patient about leprosy is the best way to manage leprosy.
  - Management includes multiple drug therapy (MDT) and compliance awareness of reactions and prevention of disability.
  - Treatment with MDT can prevent the disfigurement and neurologic disability associated with leprosy.
- **Prognosis**
  - Prognosis depends on the stage of the disease at diagnosis as well as on the initiation and compliance with MDT.
  - Relapse of leprosy after treatment with MDT is rare.
  - **Complications** – Are the result of nerve damage causing anesthesia and weakness. They occur if not treated early and include painless injuries mutilation, claw hand, foot drop, and reversal reactions. The resultant deformity and disability leads to hideous disfigurement.

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Abbreviations

AFB, Acid-fast bacilli; BB, Mid-borderline; BL, Borderline lepromatous; BT, Borderline tuberculoid; ENL, Erythema nodosum leprosum; HRUS, High resolution sonography; I, Indeterminate; LL, Polar lepromatous; LLON, Leprosy late-onset neuropathy; M, Mycobacterium; MB, Multibacillary; MTD, Multidrug therapy; NGO, Non-governmental organizations; NHDP, National Hansen's Disease Programs; PB, Paucibacillary; PNL, Pure neuritic leprosy; TNF, Tumor necrosis factor; TT, Polar tuberculoid leprosy

9.1 Introduction

Leprosy (alias Hansen's disease) is one of the world's oldest and most dreaded diseases that still continues even today to be associated with significant social stigma. The stigma is mainly because of the hideous deformities it produced. Leprosy is essentially neural at inception and there is no non-neural leprosy. It is one of the most common treatable peripheral neuropathy in the world. Although leprosy can be effectively treated with multidrug therapy (MDT), many patients continue to develop disabilities after therapy. Patients with leprosy have high rates (56 %) of established nerve damage at diagnosis, which frequently lead to disability despite treatment with steroids [1, 2]. In view of the high prevalence rate in many parts of Asia, and with increasing globalization, physicians practicing in both high and low endemic areas should have acute awareness of the possibility of leprosy, and be familiar with its varied presentations. Early diagnosis and management are necessary to minimize the likelihood of these disabilities [3].

9.2 Epidemiology

Leprosy is an important global public health problem. The prevalence of leprosy is variable, and majority of cases are found in developing countries. In the past two decades, combined efforts from the World Health Organization (WHO), local governments, health professionals, and nongovernmental organizations (NGOs) in identifying and treating patients with leprosy has resulted in its near elimination [4]. Multidrug therapy (MDT) has been the main weapon against leprosy since its inception in 1981. Between 1985 and 2010, the prevalence rate per 10,000 fell from 21.1 to 0.37 excluding Europe [5]. European countries also have sporadic cases mostly involving immigrants and also few native residents [6]. India achieved the target of elimination of leprosy in 2005, a major milestone not only for India but globally [7]. India, Brazil, Indonesia, Bangladesh, and Nigeria top the 16 countries reporting more than 1000 new cases annually in 2009 [5]. With increasing international travel, however, patients with leprosy may present anywhere. Active case-finding studies record more cases than are believed to exist in the area by passive case-finding alone [8].

9.3 Clinical Classification

Although leprosy primarily affects skin and peripheral nerves, many consider it to be a disease of the peripheral nerves. Hosts' cellular immune response to *Mycobacterium leprae* determines the various clinical forms. Ridley Jopling classification is based on clinical, histological, and immunological criteria [9]. It divides leprosy into polar tuberculoid (TT) (increased cell-mediated immunity); polar lepromatous (LL) (selective inability to mount cellular immunity to *M. leprae*); broad borderline category between TT and LL, subdivided into borderline lepromatous (BL); mid-borderline (BB); borderline tuberculoid (BT); and a minor indeterminate (I) form usually observed in the setting of contact investigation, often in children, which may heal spontaneously.

The WHO classification system is based upon the number of skin lesions present: paucibacillary leprosy (PB) (5 or <5 skin lesions); single lesion PB form; and multibacillary leprosy (MB) (6 or >6 lesions). Peripheral nerve thickening is not taken into account. Counting skin lesions alone may lead to misclassification of many patients as PB leprosy rather than MB leprosy, leading to undertreatment in some cases.

9.4 Main Clinical Features

Dermatological and neurological manifestations are the main feature.

9.4.1 Skin Lesions with Sensory Impairment

Hypopigmented or erythematous patches/plaques with hypo- or anesthesia are often the first clinical sign of the disease.

9.4.2 Neurological Features

It is important to remember certain principles regarding the neural aspects of leprosy:

1. Histopathological evidence of intradermal nerves is invariably present with clinical manifestations of sensory changes in the skin patch.
2. Thickened cutaneous nerves with sensory changes in the area they innervate do occur frequently without detectable enlargement of major nerve trunks.
3. Sensory neuropathy invariably precedes motor damage. Sensory deficit can manifest at any site while motor deficit is restricted to selected nerves and distal muscles, proximal muscles being spared.
4. Mode of spread of *M. leprae* after entry through epidermis is centripetal.
5. The deformities and physical disabilities are consequent of nerve damage that continue to occur even after the chemo-treatment is complete.
6. Leprosy affects mainly those areas of the skin, which have a relatively lower temperature and are more exposed to trauma.

Neural involvement may follow, or occur concurrently, or without cutaneous lesions. The neural manifestations include sensory, autonomic, and motor symptoms. Sensory clinical presentations are the most common and usually open the clinical picture by the decrease or absence of sensation in the earliest diagnostic lesions. Small-fibers neuropathies predominate, mainly in the early stages. Large fibers are involved later or, in specific cases, can predominate. Rarely a predominant motor involvement may be the presentation. Leprosy presentations include mononeuritis, mononeuritis multiplex, and polyneuritis.

Mononeuritis is the most common presentation of leprosy, and nerves in the upper limbs are more often affected. The most commonly involved nerves are the ulnar, median (claw hand), the common peroneal nerve (foot drop), the posterior tibial nerve (claw toes and plantar insensitivity), the facial nerve (lagophthalmos), the radial cutaneous nerve, and the great auricular nerve (Fig. 9.1). In patients with tuberculoid disease, sensory and/or motor loss generally occurs in the distribution of nerves in the vicinity of the skin lesion; in patients with lepromatous disease nerve damage may become more generalized.

Cranial neuropathy in leprosy is not rare. There is clinical evidence of cranial nerve involvement in 18 % of patients with leprosy. Leprosy can affect any cranial nerve (2–12th) isolated or in combination with fifth and seventh cranial nerves being the commonest. It is more common in MB form accounting for 10–22 % of cases. Cranial neuropathy occurs at any stage and may be the presenting feature of leprosy (Fig. 9.2).

Distal neuropathy affecting exteroceptive sensation, due to a confluent mononeuritis multiplex, and without muscle weakness may be the presentation in leprosy. Symmetrical neuropathies out-

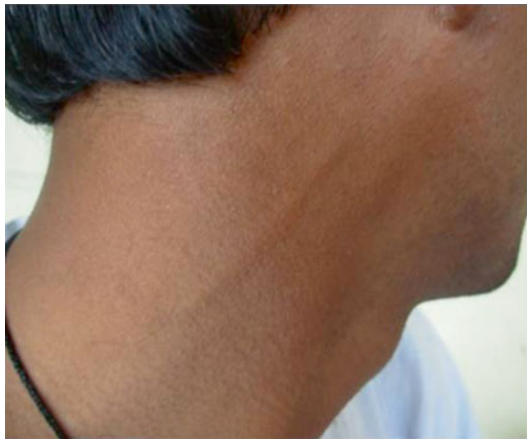

Fig. 9.1 Thickened great auricular nerve in a patient with borderline tuberculoid leprosy

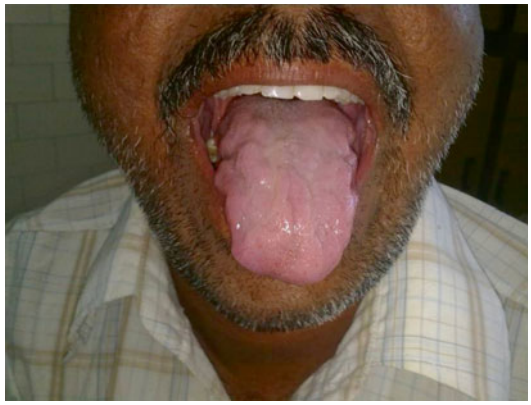

Fig. 9.2 Bilateral involvement of the 12th cranial nerve in a patient with pure neuritic leprosy

numbered mononeuritis multiplex (12 versus 7, respectively) in a series of 19 patients, presenting with proprioceptive loss in leprous neuropathy [10]. More proximal involvement in the form of a spinal cord granuloma has been reported [11]. Sensory nerve damage is accompanied by autonomic involvement.

Neuropathic pain due to small-fiber damage is a well-recognized feature of leprosy neuropathy occurring in 45.8 % of cases. Painful symptoms were also seen in 42.1 % of pure neuritic leprosy (PNL) patients [12]. Rarely leprosy can present with painful neuropathy later in the course of the disease [13].

Pure neuritic leprosy (PNL) Clinical case series estimate that 4–8 % of all leprosy is limited to the peripheral nerves [14, 15] without skin lesions. The clinical presentation is mononeuritis or mononeuritis multiplex. The clinical features of leprotic nerve involvement include nerve enlargement, tenderness, and pain and sensory (painless burns, ulcers) and motor impairment.

Late onset neuropathy Relapses occur in the form of late reversal reaction or due to reinfections. Rarely delayed nerve impairment years after MDT occurs, which cannot be explained by relapses or reactions. Presentation may be an acute mononeuropathy or a chronic and slowly progressive multiple mononeuropathy or polyneuropathy. This form is a leprosy late-onset neuropathy (LLON) [16]. Probably it represents an immune reaction due to the persistence of the bacillus antigen.

9.4.3 Complications

Complications of leprosy arise as a result of nerve damage leading to deformity and disability which could be physical or functional disability. Claw hand, foot, or wrist drop, lagophthalmos, is the late complications of nerve damage. The other ones are collapsed nose, or perforated nasal septum, ulceration, osteomyelitis, contractures, mutilation, and blindness. This occurs through loss of pain perception leading to trauma, burns, tissue damage, injury, and secondary infection. Progressive disfigurement ensues.

Leprosy related nerve damage is immune mediated and may start before diagnosis, during treatment, or even after completion of treatment. *Reversal reactions (type 1 reactions)*, an important complication of leprosy, are episodes of acute inflammation affecting skin and nerves occurring when a patient develops increased cell-mediated immunity toward *M. leprae* and moves toward the tuberculoid end of the leprosy spectrum. The histological features of reversal reactions include edema, lymphocytic infiltration, and giant cell formation. The outcome of this cellular activation is the elimination of leprosy

bacilli. The acute inflammatory response is seen at the sites of localization of *M. leprae* (i.e., skin and peripheral nerve), and manifests clinically as inflammatory skin lesions and acute neuritis. These reactions occur either before treatment (some patients initially present for medical attention in the setting of a reaction), during treatment, or months to years after treatment has been completed and may affect 30–50 % of all leprosy patients [17].

Erythema nodosum leprosum (ENL) (*type 2 reaction*) is an acute inflammatory condition involving a tumor necrosis factor (TNF)-alfa and immune complex mediated immune response with infiltration of Th2-cells. Nodules and painful, raised red papules are characteristic. Other accompanies are uveitis, iridocyclitis, episcleritis, neuritis, arthritis, dactylitis, lymphadenitis, and orchitis. Fever, prostration, anorexia as well as other symptoms are frequent. Neurological deficits in uncomplicated leprosy evolve slowly in contrast to neuritis during reactions. The nerves affected in the reactional leprosy are the same as in progressive leprosy.

9.4.4 Diagnosis

The diagnosis of leprosy is primarily a clinical one, and early diagnosis is crucial to management. Three cardinal signs have remained the basis for the clinical diagnosis of leprosy:

Anesthetic/hypoanesthetic skin lesion(s)
Thickened peripheral nerve(s) with impairment of sensations in the area supplied
Acid-fast bacilli in the skin smear

Anesthetic skin lesion(s) The sensitivity and specificity of anesthetic/hypoesthetic lesion as a diagnostic test varies. High figures for the sensitivity of this test among PB patients were reported from India (93 %) [18], Bangladesh (92 %) [19], and Ethiopia (86 %) [20]. In MB leprosy, 74 % of patients who had skin lesions with normal sensation were smear-positive, thus representing potential source of *M. leprae* in the community. The clinical implication is, by utilizing anesthesia over the skin patches as the single criterion, almost 30 % of leprosy patients may be missed, most of whom will be smear positive [21].

Thickened peripheral nerve(s) Nerve thickening in neuritic leprosy ranges from 40 to 75 %. Incidence of thickened nerves in leprosy varies in various reported series. Nonspecific enlargement of a nerve seen in some heavy manual workers may lead to false positive findings [22].

Slit skin smears Skin smears 100 % specificity. However the sensitivity of this single examination is low, because only about 10–50 % of all patients are smear positive [21].

9.4.5 Histopathology

Biopsy is the gold standard diagnostic method especially in pure neuritic leprosy and LLON but is not feasible with the major peripheral nerve trunks involved in leprosy. Other limitations of nerve biopsy include: inability to distinguish relapse from reaction in treated PB patients or to differentiate them from other granulomatous diseases like sarcoidosis, tuberculosis, and noninfective foreign body granuloma despite high specificity of histopathology.

Simple histological examinations of nasal mucosa and dermatologically normal skin from hyperesthetic regions may reveal the characteristic changes of leprosy [23–25].

Fine needle aspiration cytology have been shown to maintain a high diagnostic yield when compared with standard biopsy and with the least side effects [26].

Serology and molecular diagnostic methods Antiphenolic *glycolipid* I (PGL-I) antibodies dosage as a diagnostic serological test has been extensively evaluated in the diagnosis of leprosy. The disadvantages of this assay is its low sensitivity especially in PB leprosy [27], inability

to diagnose early cases and its low predicting value in identifying who will develop the disease in future [28].

Polymerase chain reaction are potentially highly sensitive and specific, but since they require a sophisticated laboratory set up, they are not currently applicable in resource poor countries except as a research tool [29].

(ND)-O-Bovine serum antigen (ND-O-BSA) based ELISA was recently found to be useful in screening of early infection with *M. leprae* and predicting/monitoring relapse [30]. However, their application in most leprosy endemic countries of the world are limited both due to lack of infrastructure and financial resource.

9.4.6 Imaging

High resolution sonography (HRUS) *and color Doppler imaging* have proven to be useful in the context of leprosy [31–33]. Since the hallmarks of leprosy are nerve enlargement (epineurial and endoneurial thickening) and inflammation, HRUS and color Doppler imaging can be used to demonstrate nerve enlargement and inflammation. HRUS detects extensive nerve damage that clinically suspected.

Magnetic resonance imaging of nerves is more sensitive than HRUS with good spatial resolution and show involvement of proximal nerves and spinal cord. Both are noninvasive, but MRI is expensive whereas HRUS is least expensive and can be repeated to monitor response to treatment as always.

9.4.7 Genetics

Several genes have been associated with a susceptibility to leprosy. The results of genome-wide analyses and candidate gene studies suggest an independent genetic control over both susceptibility to leprosy per se and development of clinical subtype. Alleles of the PARK2/PACRG gene [34], as well as other genes [35], are supposed to determine the innate immunity. Variants of genes in the NOD2-mediated signaling pathway (which regulates the innate immune response) were found to be associated with susceptibility to leprosy [36] in patients from China. Cells of monocyte/dendritic cell origin may play a role in the pathogenic mechanisms of this immunity. The cellular immune response appears to be controlled by a number of non-HLA genes [37, 38]. It is difficult to discern the relative contribution of genetic factors following exposure.

9.5 Differential Diagnoses

9.5.1 Patients Presenting with a Patch of Sensory Loss

Characteristic pattern of sensory loss in leprosy involves patchy area along nerves with loss of sweating/hair and sparing of proprioceptive sensations. Other situations which can mimic this pattern include early radiculopathy and conditions affecting cutaneous nerve twigs and entrapment palsies. In lower limb entrapment neuropathies with cutaneous sensory loss mimicking Hansens' disease include meralgia paresthetica, genitofemoral nerve at the inguinal region. Enquiry about any precipitating factors for the likely compression of the nerve would help. The clue may be obtained in the occupation.

9.5.2 Distal Symmetrical Sensory Loss

Other conditions like hereditary sensory neuropathy type I and III, Tangier's disease, amyloidosis, and some cases of diabetic neuropathy need exclusion. In polyneuropathies, the sensory deficit is classically in glove and stocking pattern. In contrast, affection in leprous neuritis is not truly distal as it affects cooler areas of the body. Cauda equina syndrome and a central cord lesion like syringomyelia may mimic leprous neuropathy.

9.5.3 Patients with Nerve Thickening

Thickened nerves are also seen in hereditary sensory motor neuropathy I, Dejerine-Sottas disease, neurofibromatosis, Refsum's disease, neoplastic infiltration, and chronic inflammatory demyelinating neuropathy. But in these diseases, the nerves are not as large, and hypertrophy is more diffuse than the localized temperature linked pattern in leprosy.

9.6 Therapy

Treatment of leprosy with multiple drug therapy (MDT) prevents development of resistance. MDT is effective and quickly renders the patient bacteriologically cured. First-line medications include dapsone, rifampin and, for lepromatous disease, clofazimine. Initially duration of treatment as recommended by WHO was 6–12 months for TT and BT and 24 months for BB, BL, and LL. Subsequently in 1998, it was reduced to 6 months and 12 months, respectively [39]. However, shorter treatment regimens have been associated with a greater incidence of relapse [40]. Therefore, the National Hansen's Disease Programs (NHDP) in the USA continues to recommend the longer duration of therapy; NHDP also advocates daily rather than monthly administration of rifampin recommended by the WHO.

Alternative agents for treatment of leprosy include minocycline, ofloxacin, levofloxacin, clarithromycin, and moxifloxacin. Evidence for the efficacy of newer drug combinations or shorter regimens is weak [41, 42].

9.6.1 Treatment of Reactions

In general, antimicrobial therapy should be continued in the setting of immunologic reactions. Mild reactions without neuritis, ulceration, or other severe symptoms can be managed with supportive care. Neuritis must be treated aggressively to prevent or minimize nerve injury and subsequent deformity and disability.

Corticosteroids (40–60 mg/day) remain the cornerstone in the treatment. Neural functions improve in 60–70 % of patients after steroid treatment but it may remain impaired in patients with preexisting or recurrent neuritis. About one-third of impaired nerves do not improve with corticosteroid treatment. Treatment is best individualized; in some cases even higher doses and longer duration of prednisone may be required [43]. Prophylactic corticosteroid treatment for prevention of neuritis has no long-term benefit. Use of prednisone should prompt reduction in rifampin dose from 600 mg daily to 600 mg once monthly. Type 2 reaction may require a relatively short course, but the reaction can recur and intermittent symptoms may continue for a year or more. Cyclosporine may be a useful second line treatment for severe type 1 reactions in patients not responding to or unable to take corticosteroids.

Clofazimine is generally increased to a dose of 300 mg daily for 4 weeks and tapered slowly after response to 100 mg/day within 12 months in type 2 reaction.

No consistently beneficial effects are seen with cyclosporine, azathioprine, methotrexate, pentoxifylline, and mycophenolate mofetil, or intralesional injection of recombinant interferon gamma and TNF alpha in treatment of type 2 reaction.

Thalidomide is very effective in treating type 2 leprosy reactions [44], but teratogenicity limits its use in women of childbearing age. Thalidomide is administered initially in a dose of 300–400 mg daily; frequently this regimen controls the reaction within 48 h. Subsequently, the dose should be tapered to a maintenance level, generally around 100 mg daily; every few months attempts are made to taper off the drug. Thalidomide may be continued for several years. Development of neuropathy should prompt immediate discontinuation. Management of the Lucio phenomenon (necrotizing vasculopathy in patients with long-standing untreated lepromatous leprosy) requires antimicrobial therapy and corticosteroids as well as skin and wound care.

Rarely, resistant cases were seen among patients with relapsed infection. Molecular techniques are available for the identification of several mutations associated with resistance to individual agents [45, 46].

Relapse of leprosy is relatively rare, and must be distinguished from immunological reaction (which is more common). The WHO has reported a slowly increasing trend in the number of relapses, with 3120 cases worldwide in 2009 (1.3 % of the number of new cases reported) [5]. Relapse rates range from 0 to 2.5 % in paucibacillary disease to 0–8 % in multibacillary disease. Most relapses occur 5–10 years after completion of treatment. Relapse is more likely to occur in the setting of incomplete treatment or a very high bacterial load at the onset of treatment. Relapse can be distinguished from immunologic reaction in that the latter should improve after a short course of prednisone. In general, treatment consists of reinitiating the same regimen used for initial therapy.

Disease progression that occurs during therapy is almost always due to nonadherence to treatment. Motor loss resulting in deformities may require corrective surgery and rehabilitation.

9.7 Prognosis

Epidemiological data on disability are not available, but they are likely to be higher than that depicted by incidence rates alone. MDT does not stop the inflammatory impairment of nerve function. Although immunosuppressive treatment may reduce the risk of new immune-mediated neuropathy, the consensus is that steroids may not be very effective if nerve impairment has lasted for more than 6 months. Progressive loss of thermal pain touch sensitivity, and more advanced stages of paralysis leads to significant disability. When these complications are identified early, before the presence of more severe nerve damage, disability can be avoided. Physical disability affects approximately 23.0 % of leprosy patients after discharge. Recovery from neurologic impairment is limited, but skin lesions generally clear within the first year of therapy.

The delay in diagnosis is an independent risk factor for the presence of physical disability at diagnosis. Physical therapy, reconstructive surgery, nerve and tendon transplants, and surgical release of contractures have all contributed to increasing the functional ability in patients with leprosy. The current global goal for reduction of the leprosy burden is to reduce number of new cases diagnosed with grade two disabilities of, at least, 35 % by the end of 2015. It will also contribute the correct and timely diagnosis of new cases before the development of disabilities and neural complications and will work to reduce the social and economic impact on the lives of individuals affected by the disease.

At the end, leprosy is still considered a serious public health issue in developing countries. It presents various clinical forms that are determined according to levels of cellular immune response to *Mycobacterium leprae*. It has varied clinical manifestations mimicking several other disease states. Clinical examination is the mainstay for the diagnosis alongwith lab design. Diagnosis of PNL is most challenging and imaging and biopsy is of great value. Neural complications lead to significant disability which mandates an early diagnosis and treatment as this is known to reduce the disability if not completely.

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Prion Diseases

10

Giuseppe Di Fede and Fabrizio Tagliavini

Key Facts

- **Definitions** – Prion diseases, transmissible spongiform encephalopathies, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease, fatal insomnia, kuru, variably protease-sensitive prionopathy.
- **Pathogenesis** – Conversion of the host-encoded PrP^{C} to an abnormal isoform, termed PrP^{Sc} which is insoluble and protease-resistant, and progressively accumulates in the CNS. PrP^{Sc} deposition in brain tissue results in neurodegeneration and glial activation.
- **Demographics** – Incidence: 1.5/million people per year.
- **Clinical features** – Phenotypically heterogeneous fatal neurodegenerative disorders characterized by cognitive decline, cerebellar, pyramidal, extrapyramidal, sensory or psychiatric disturbances, seizures, and myoclonus.
- **Diagnosis**
  - **Laboratory**
    - **CSF** – Detection of 14.3.3 and high levels of total tau in CJD.
    - **Genetics** – Mutations in the *PRNP* gene and codon 129 *PRNP* genotype.
  - **Imaging** – MRI – DWI: hyperintensity in the cerebral cortex and/or striatum and, less frequently, in the thalamus in CJD.
  - **Neurophysiology** – From nonspecific slowing of background activity to disease-typical periodic sharp wave complexes at EEG, and abnormalities of electroretinogram and visual evoked potentials in CJD.
  - **Other in vivo tests** – Tonsil biopsy in variant CJD.
  - **Pathology and biochemistry on brain tissue** – Spongiform changes, neuronal loss, and astrocytic gliosis in the cerebral cortex and subcortical gray structures in CJD. PrP amyloid plaques and severe thalamic degeneration, in Gerstmann-Sträussler-Scheinker disease and fatal familial insomnia, respectively. Detection of abnormal PrP in the CNS by immunohistochemistry and western blot analysis).
- **Therapy** – No disease-modifying treatments available.
- **Prognosis** – Invariably fatal outcome. Mean survival from few months to several years.

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Abbreviations

BSE, Bovine Spongiform Encephalopathy; CJD, Creutzfeldt-Jakob disease; DWI, Diffusion weighted imaging; ERG, Electroretinogram; fCJD, Familial CJD; fFI, Familial FI; sFI, Sporadic fatal insomnia; FLAIR, Fluid-attenuated inversion recovery; GSS, Gerstmann-Sträussler-Scheinker disease; iCJD, Iatrogenic CJD; M, Methionine; MRC, Medical Research Council Prion Disease Rating Scale; MRI, Magnetic resonance imaging; PrP, Prion protein; PrP^{C}, Normal prion protein ; PRNP, Prion protein gene; PSWCs, Periodic sharp wave complexes; RT-QuIC, Real-time quaking-induced conversion; Sc, Scrapie; sCJD, Sporadic CJD; sFI, Sporadic FI; TSEs, Transmissible Spongiform Encephalopathies; V, Valine; vCJD, Variant CJD; VPSPr, Variably Protease-Sensitive Prionopathy.

10.1 Definition

Human transmissible spongiform encephalopathies (TSEs) or prion diseases are a group of fatal neurodegenerative disorders that includes kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), sporadic and familial fatal insomnia (*FI*), and variably protease-sensitive prionopathy (VPSPr).

Human prion diseases can be divided etiologically into:

- Inherited forms: familial CJD (*fCJD*), familial FI (*fFI*), GSS
- Sporadic forms: sporadic CJD (*sCJD*), sporadic FI (*sFI*), VPSPr
- Acquired forms: iatrogenic CJD (*iCJD*), variant CJD (*vCJD*), kuru.

10.2 Pathogenesis

The central event is the conversion of the host-encoded cellular prion protein (PrP^{C}) into an abnormal isoform designated PrP^{Sc} (Sc = *Scrapie*, prion disease in sheep and goats). This transition involves a conformational change with decreased alpha-helical and increased beta-sheet content that confers PrP^{Sc} with partial resistance to proteolytic degradation. According to the "prion hypothesis", the progressive accumulation of PrP^{Sc} is sustained by a self-propagating process in which PrP^{Sc} interacts with and converts PrP^{C} into the abnormal PrP^{Sc} isotype [1, 2]. PrP^{Sc} deposition is associated with distinctive neuropathological changes.

Approximately 10–15 % of human prion diseases are associated with autosomal dominant pathogenic mutations in the prion protein gene (*PRNP*) [3]. In most instances, the genetic defect is thought to increase the propensity of the protein to form PrP^{Sc} [3]. Polymorphism at codon 129 of *PRNP* – encoding either methionine (M) or valine (V) – strongly affects susceptibility to sporadic and acquired forms of disease and influences phenotypic expression of most human prion diseases [3, 4]. About 38 % of Europeans are homozygous for the more frequent methionine allele, 51 % are heterozygous, and 11 % are homozygous for valine. Homozygosity at *PRNP* codon 129 predisposes to the development of sporadic and acquired CJD [3].

Several human PrP^{Sc} types have been identified, based on protease-resistant fragments of different sizes and different glycosylation patterns detected by western blot analysis of brain homogenates (Fig. 10.1). These differences suggest the existence of several human PrP^{Sc} conformers which may be responsible for the occurrence of distinct disease phenotypes [5]. The biochemical properties of different prion conformers are retained after transmission to experimental animals of both the same and different species, suggesting the presence of prion strains, each characterized by specific biological properties (i.e., they produce distinct incubation periods and patterns of neuropathological changes in inbred mouse lines) [3].

10.3 Demographics

TSEs are rare in human beings. The overall incidence is approximately 1.5 per million people per year.

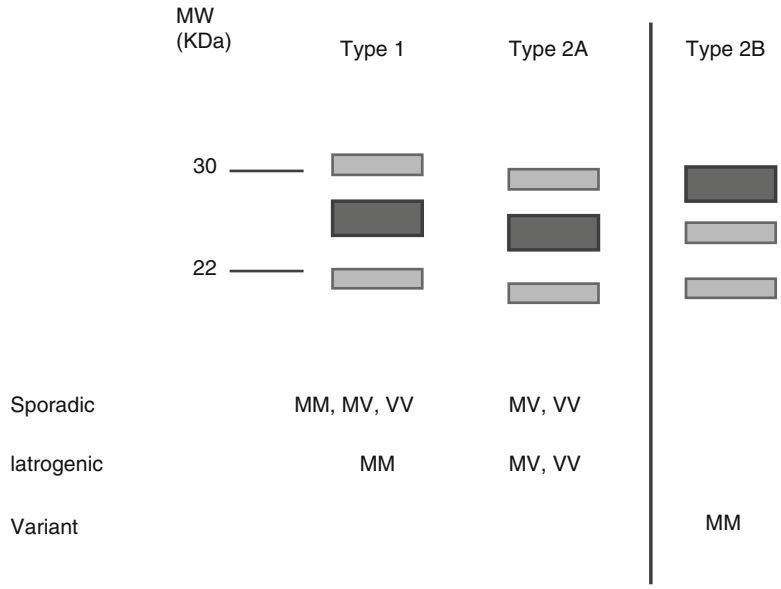

Fig. 10.1 Molecular strain types of Creutzfeldt-Jakob disease (CJD). Schematic representation of distinct PrP^{Sc} conformers associated with CJD. PrP^{Sc} types are identified, based on the different fragment sizes seen on western blots, after treatment with proteinase K, and on the different glycosylation pattern (i.e., the proportion of di-, mono-, and unglycosylated fragments of the PrP). PrP polymorphism at residue 129 [methionine (M) or valine (V)] contributes to genetic susceptibility to both sporadic and acquired forms. Box sizes represent the relative difference in intensity of the three PrP glycoforms

- *sCJD* – It accounts for 80–85 % of human TSEs. The incidence is equal in men and women [6].
- *VPSPr* – It accounts for about 2–3 % of sporadic prion diseases, but many cases of VPSPr are not clinically recognized [7].
- *Inherited prion diseases* – Approximately 10–15 % of human prion diseases are associated with autosomal dominant *PRNP* mutations [3].
- *Kuru* – It affects the Fore people of the Eastern highlands of Papua New Guinea, due to the diffusion of cannibalism in postmortem rituals. Today only a few cases of kuru are seen.
- *vCJD* – It is the human form of bovine spongiform encephalopathy (BSE). vCJD affects younger individuals than sCJD (typically age 14–50 years). Primary infection in vCJD occurs by oral route, via meat products contaminated with the BSE agent [8].
- *iCJD* – Prions have been transmitted by human growth hormone and gonadotropin prepared from cadaveric pituitary glands, by corneal and dural grafting, and by brain electrodes; such cases are rare [8].

10.4 Clinical Features

sCJD Classical sCJD presents as rapidly progressive dementia usually with myoclonus. Additional neurological features include pyramidal and extrapyramidal signs, cerebellar ataxia, and cortical blindness. The onset is usually in the 45–75 years age group with median age at death of 68 years [3]. The clinical evolution is typically over weeks, progressing to akinetic mutism with a median disease duration of 5 months.

Atypical forms of sCJD are well recognized. Ten percent of CJD cases have a much more prolonged clinical course with a disease duration of over 2 years, and may present with cerebellar ataxia rather than cognitive impairment (*ataxic CJD*), extensive degeneration of the cerebral

white matter in addition to spongiform vacuolation of the gray matter (*panencephalopathic CJD*), or prominent early muscle wasting (*amyotrophic CJD*) [3].

The molecular determinants of this heterogeneity are the M/V polymorphism at codon 129 of PRNP and the type of PrP^{Sc} that accumulates in brain tissue. Indeed, more than 90 % of patients with sCJD who are 129-MM have type 1 PrP^{Sc}, whereas more than 80 % of patients who are 129-VV and 129-MV have PrP^{Sc} type 2A (Fig. 10.1). Grouping of all cases of sporadic prion diseases according to the pairing of the 129 genotype with the PrP^{Sc} type results in the recognition of six disease subgroups, five presenting with a sCJD phenotype (sCJDMM1/sCJDMV1, s*CJDMV2,* s*CJDVV1,* s*CJDVV2, sCJDMM2 "cortical"*) and one occurring with the features of sporadic fatal insomnia (s*CJDMM2 "thalamic"*). These subgroups actually match most clinical subtypes previously described [7].

VPSPr The most common clinical presentation involves a triad consisting of psychiatric signs (psychosis or behavior and mood changes), speech deficit, and cognitive decline often with prominent involvement of frontal lobe functions. Progressive motor impairment, especially parkinsonism and ataxia, are succeeding features along the course of the illness [7].

Inherited prion diseases (fCJD, GSS, fFI) Traditionally, inherited prion diseases have been classified by the presenting clinical syndrome, falling into three main subdivisions of either CJD, FI, or GSS. Extensive phenotypic variability in inherited prion diseases occurs even in family members with the same *PRNP* mutation [3, 9].

The clinical and neuropathological phenotype of fCJD widely overlaps that of sCJD. GSS is an autosomal dominant neurodegenerative disease caused by missense (P102L, P105L, A117V, F198S, D202N, Q212P, Q217R) or insertional *PRNP* mutations [9] and classically presents as a chronic cerebellar ataxia with pyramidal features, while dementia usually occurs later in a clinical course that is typically longer than in classical CJD.

FFI is characterized by progressive untreatable insomnia, dysautonomia, motor abnormalities, and dementia. Disruption of the circadian oscillations of endocrine functions are observed early in the disease. FFI is linked to the D178N mutation in PRNP associated with methionine at codon 129 and is neuropathologically characterized by rather selective thalamic degeneration.

Acquired prion diseases – iCJD The clinical phenotype of iCJD is influenced by the route of exposure. In cases with inoculation into the central nervous system – for example, via neurosurgical instruments – the clinical features are indistinguishable from sCJD. Peripheral route of infection, such as human pituitary hormone treatment, is initially marked by a progressive cerebellar syndrome, while other focal signs such as myoclonus usually develop later [10].

vCJD vCJD presents as a progressive neuropsychiatric disorder (chronic depression, social withdrawal, psychotic features) with peripheral pain or dysesthesia followed by cognitive decline and ataxia. A number of patients also develop chorea or dystonia and less commonly myoclonus. Progression is less rapid than in sCJD [7].

Kuru The clinical course of the disease is characterized by a progressive cerebellar ataxia associated with tremors. Dementia is late and may be absent [3].

10.5 Diagnostic Markers

- *MRI.*
  - CJD: Brain atrophy is a common but late finding. Signal hyperintensity at diffusion weighted imaging (DWI) is detected in the neocortex and striatum in more than 65 % of sCJD patients, in the neocortex alone in less than 20 %, and in the striatum alone in 10 %. Other regions, such as the thalamus, can also be involved. The sensitivity and specificity of DWI are over 90 % [7, 11].

  - The most pronounced signal enhancements in vCJD are observed in the posterior thalamus ("pulvinar sign"). This signal pattern is present in 78 % of the vCJD cases [12].
  - GSS – Neuro-imaging may be normal or show nonspecific atrophy affecting the cerebral hemispheres and/or cerebellum.
  - FI – Aspecific changes.
- *PET*: Thalamic hypometabolism, with variable participation of cerebral cortical regions in FI [7].
- *CSF*
  - sCJD and fCJD patients bearing the E200K and V210I mutations: detection of 14-3-3 in the CSF is valuable for the diagnosis, although high variable values of specificity and sensitivity have been reported [13].
  - fFI – 14-3-3 is absent.
  - GSS – detection of 14-3-3 is uncommon.
  - iCJD – sensitivity of the test is lower (60 %).
  - vCJD – only half of the patients have elevated 14-3-3 levels.
  - VPSPr – 14-3-3 test is negative in most cases [7].

It is noteworthy that 14-3-3 is expected to be increased also in other acute illnesses with extensive neuronal damage [12].

Tau protein is usually elevated in CSF of CJD patients, with specificity ranging from 40 to 67 % and sensitivity 87 % [13].

The *real-time quaking-induced conversion* (*RT-QuIC)* is a CSF test with sensitivity greater than 83–87 % and 100 % specificity. It is based on rapid detection of minute amounts of PrP^{Sc} by *in vitro* conversion of recombinant PrP^{C} [14].

- *Genetics* – 10–15 % of human prion diseases are associated with autosomal dominant mutations in *PRNP*. Over 30 pathogenic mutations have been described [2].
- *EEG* – From nonspecific changes in early stages to periodic sharp wave complexes (PSWCs) in middle and late stages of sCJD and fCJD. The EEG is not informative in iCJD and vCJD. PSWCs are not constant features in VPSPr and are usually absent in FI and GSS [12].
- *Visual evoked potentials (VEPs) and electroretinogram (ERGs)* – Definite, though nonspecific abnormalities in CJD patients [15]:
  - *VEPs* – From deteriorated to enlarged cortical responses;
  - *ERGs* – B-wave attenuation/prolonged latencies, flicker deterioration, and attenuation of oscillatory potentials.
- *Polysomnogram* – Reduction of sleep-related EEG activities, even in the early phase of the disease in FI.

Tonsil biopsy in vCJD enables to detect PrP^{Sc} deposition in lymphoreticular tissues. Promising tests include *detection of* PrP^{Sc} *in the olfactory mucosa* of sCJD patients by *RT-QuIC*, and in extra-neural tissues – including urine – of vCJD patients by protein misfolding cyclic amplification technology (PMCA) [16].

10.5.1 Pathology and Biochemistry on Brain Tissue

Neuropathological examination on autopsy-derived material and identification of the abnormal isoforms of prion protein by western blot analysis are required for a definite diagnosis. The histological triad of CJD and kuru includes spongiform changes in the gray matter, nerve cell loss, and astro- and micro-gliosis. The definitive histological diagnosis is made by the immunohistochemical demonstration of the disease-related form of PrP in the brain [17]. Several patterns of PrP^{Sc} deposition may be associated with distinct types of prion disease: florid plaques are typical of vCJD cases; amyloid deposits accumulate in the brain of GSS patients; and different pattern of PrP^{Sc} accumulation (i.e., synaptic, coarse/perivacuolar, plaque-like, and perineuronal) have been described in sCJD [17], while in FI it is hard to detect PrP^{Sc} deposits by immunohistochemistry.

Detection of the abnormal isoforms of PrP by western blot is necessary for a definite diagnosis of prion disease in humans. Three major types of human PrP^{Sc} associated with sporadic and acquired CJD can be differentiated on immunoblots after proteinase K digestion of brain homogenates

(Fig. 10.1). PrP^{Sc} types 1–2A are seen in sporadic or iatrogenic CJD brain, while type 2B PrP^{Sc} is uniquely seen in vCJD brain [3]. The higher sensitivity to protease digestion and the distinctive ladder-like electrophoretic pattern of the PK-resistant fragments are the core biochemical features of VPSPr cases [7]. sFI is associated with the 2A type, fFI with a PrP^{Sc} more similar to the 2B type. Finally, GSS cases are characterized by the presence of small size PrP^{Sc} fragments (7–10 kDa) forming amyloid structures in brain tissue [2].

10.6 Therapy

No treatment that interferes with pathogenesis or delays disease progression is available; several therapies have failed in clinical trials. A number of drugs may be used to ameliorate symptoms: clonazepam/levetiracetam for myoclonus, quetiapine for hallucinations [7].

10.7 Prognosis

Human prion diseases have an invariable fatal outcome. The most relevant modifiers of prognosis are: age at onset, sex, *PRNP* genotype (M/V polymorphism at codon 129 and pathogenic mutations), and the type of PrP^{Sc}. Additional elements come from laboratory tests (14.3.3 in CSF) and EEG findings.

sCJD A demographic study on the Italian population [18] showed that clinical duration in sCJD is influenced by sex (5.4 months in men and 7.0 months in women). The study showed also a shorter survival time in aged patients. A comparable age-specific effect on disease duration has been reported in several European countries participating to the EU collaborative study group of CJD, and in Japan, but not in Sweden and USA. The interpretation of these data remains unclear and raises doubts about unknown risk factors for sCJD. Differences in the clinical syndrome and neuropathological lesion profile have been reported between young and old patients with sCJD also in other studies, which showed a prolonged clinical syndrome in young CJD patients [19]. Several studies [18–20] remarked that methionine homozygous patients have a significantly shorter clinical duration than valine homozygous or heterozygous patients, confirming that the M/V polymorphism at codon 129 of PRNP gene is a relevant modifier of the course of sCJD.

The combination of M/V genotype at polymorphic codon 129 and the type of PrP^{Sc} results in different pathways of disease progression in sCJD cases. The most common sCJD subtype (*sCJDMM1*) [20] is characterized by short disease length (3–4 months) and a "classical" clinical presentation. In the second most common subtype (*sCJDVV2*), also described as cerebellar or ataxic variant, the duration is longer than in type 1, namely 6 months. s*CJDMV2* subtype also corresponds to an ataxic variant. Its clinical duration differs significantly from the previous subtype, with the average of 17 months. *sCJDMM2* "cortical" subtype is characterized by an average disease duration of 20 months. *sCJDVV1* is frequently referred to as "early onset sCJD" because average age at onset is 39 years, and the disease lasts over approximately 15 months. *sCJDMM2* "thalamic" is the sixth subtype. Its mean age at onset is 50 years and its mean duration is 24 months [2, 20].

An extensive study on 2,451 pathologically confirmed sCJD patients [20] showed that age at disease onset correlates significantly with a positive EEG, independent of disease duration and molecular subtype. Patients who develop symptoms <50 years have a lower rate of typical PSWCs (22 %) than patients presenting after 60 years of age.

Disease duration in patients with an atypical EEG is longer than in patients with typical EEG (6 versus 4 months).

CSF 14-3-3 test is also related to disease progression: patients with 14-3-3 proteins detectable in their CSF have shorter disease durations than cases with a negative test (median: 5 versus 11 months).

MRI results do not correlate with disease duration and are not significantly associated with age at onset [21].

Inherited prion diseases The clinical manifestations of inherited cases vary depending on the specific mutation and often the disease has earlier onset and longer duration than sCJD. The effects of the M/V polymorphism at codon 129 of *PRNP* gene are variable, being less consistent in fCJD cases associated with the E200K mutation [10]. Most *PRNP* mutations are *in-frame* with methionine. The rare cases where the mutation is associated with valine at codon 129 usually present with less severe clinical features. Also in GSS the genotype at *PRNP* codon, 129 may be a modifier of the phenotype and disease severity. In patients carrying the D178N mutation, the disease phenotype is deeply influenced by the M/V polymorphism at codon 129, resulting in fFI or fCJD when the mutation is in frame with M129 or V129 respectively [3].

Kuru Methionine homozygosity at *PRNP* codon 129 is overrepresented in younger patients, in patients with a shorter incubation period, and in patients with short duration of disease [10].

iCJD In iCJD there is an overrepresentation of homozygosity at the PRNP polymorphic codon 129. Interestingly, in iCJD caused by human growth hormone the overrepresentation is due to the V/V genotype (31 % compared to 10 % of the normal population) and not to the methionine homozygosity seen in most other CJD cases [8]. Peripheral routes of infection are typically associated with longer incubation periods [3]. The number of iatrogenic cases is diminishing due to improvement in methods of decontamination. Still, there is a threat of a "second wave" of cases carrying genotypes less prone to infection (MV or VV) that may have a longer incubation period.

vCJD vCJD patients are young (more than half have been below 40 years of age at time of death) and progression is usually slower than in sCJD cases (median 13 months; range 6–39 months from first symptoms to death). Risk factors for the development of vCJD include age, residence in the UK, and methionine homozygosity at codon 129 of PRNP. Although gene analysis of PRNP in patients with vCJD has always shown homozygosity for methionine (M/M) at the polymorphic codon 129, only time will show whether this methionine homozygosity is necessary for vCJD to develop, or whether it is just associated with a shorter incubation period [10].

VPSPr All combinations of polymorphic codon 129 (M/M, M/V, and V/V) have been reported. Those cases of 129 V/V genotype are characterized by psychiatric disturbances, cognitive changes, and different forms of aphasia. In 129-M/M and 129-M/V cases, parkinsonism, ataxia, and myoclonic jerks have been observed. The duration of disease ranges from 22 to 45 months [7].

Despite the data described above, there are still a number of uncertainties about the key factors which can effectively modulate the prognosis in human prion diseases. The lack of consensus criteria in the assessment of clinical progression and disability is a fundamental obstacle for the development of effective treatments. Patients may survive for long periods in a very advanced stage of illness or may die before reaching the end stage of disease (most often due to aspiration pneumonia). Moreover, there is a remarkable heterogeneity of disease progression between and within prion disease types. Several distinct patterns of progression are possible: rapid decline over weeks or a few months (mostly patients with sporadic CJD) and slow decline over years (almost exclusively patients with inherited prion disease). This phenotypic heterogeneity makes the assessment of disability in these patients more arduous. Existing rating scales, which are well validated in other neurological settings, are far less suited to prion diseases. For example, the Mini-Mental State Examination and Alzheimer's Disease Assessment Scale – routinely used as an outcome measure in Alzheimer's disease clinical trials – fail to capture the radical physical impairments which may be present despite preserved cognitive function during disease progression [22]. Ranked symptoms and impairments reported by caregivers of patients with prion diseases have been grouped into functional domains, including mobility, personal care/continence, communication/speech, behavior/hallucinations, eating/swallowing, and cognition/memory. Recently,

a novel scale of disability (Medical Research Council Prion Disease Rating Scale, MRC) based on the exploration of these five domains has been proposed for the assessment of disability in patients with prion diseases [22].

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Myelin Disorders: Multiple Sclerosis

11

Graziella Filippini and
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Key Facts

- **Terminology and definitions** – *MS* is a chronic immune-mediated inflammatory condition of the CNS characterized by demyelination and axonal degeneration.
- **Clinical features** – *MS* may be characterized by (1) first and single CNS attack of young adults (*CIS*), (2) recurrent exacerbations of neurological dysfunction with complete or nearly complete recovery (*RRMS*), (3) continuous worsening over at least 6 months in patients with RRMS (*SPMS*), and (4) continuous worsening from onset, minor fluctuations without true relapses; in 83 % of cases spastic paraparesis is a typical clinical picture (*PPMS*).
- **Epidemiology** – Mean age at onset of 30 years (*CIS, RRMS*). *PPMS*: Mean age at onset of 40 years, prevalence ~15 % of all MS.
- **Diagnostic markers**
  - **CSF** – Oligoclonal bands, absent from serum in 2/3 of *CIS* (present in higher % in *RR, SP, PP*); mild pleocytosis, possible in *RR*.
  - **Pathology** – focal lymphocytic infiltration and microglia activation followed by demyelination and axonal degeneration (*RR*). Prevalent neurodegenerative features (*SP, PP*).
  - **Imaging** – *CIS*: One or more hyperintense CNS lesions at T_2-MRI, (Gd ± at T_1-MRI). Multifocal CNS lesions (Gd ±) in both time and space (*RRMS*). Brain T1-hypointense alterations as marker of neurodegeneration (*SPMS, PPMS*). Brain/spinal cord atrophy, very rare Gd + lesions (*PPMS*).
  - **Neurophysiology** – Delayed or absent VEP; pathological multimodal evoked potential (*MS*).
- **Top differential diagnoses** – NMO, ADEM, CNS vasculitis and CNS lymphoma.
- **Prognosis**
  - **Principles of treatment** – Intravenous corticosteroids, immunomodulatory or immunosuppressive treatments for RRMS. No useful disease-modifying treatments for *SPMS* or *PPMS.*
  - **Disability** – A second neurological episode occurs in 17–45 % within 2 years, 50 % in 5 years, 60 % in 10 years and 68 % in 14 years from onset (*CIS*). Chronic course evolving over 30–40 years; 30 % of patients remain

(continued)

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Key Facts (continued)

fully ambulatory after 20 years, 80 % develop SPMS 20–25 years after onset (*RR*). Wheelchair bound in 15–25 years (*SP*). At 7 years from onset, 1/4 of patients require assistance to walk; 25 % walk independently after 25 years (*PPMS*).

– **Mortality** – Suicide and mortality substantially increased in all MS variants (in *PPMS* ~3 % of deaths are due to suicide). Median time to death: 35–50 years from onset for *SPMS*; 33 years for *PPMS*.

Abbreviations

CIS, clinically isolated syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; DIS, dissemination in space; DMDs, disease modifying drugs; EDSS, Extended Disability Status Scale; Gd, gadolinium; LSE, systemic lupus eritematosus; MRI, magnetic resonance imaging; MS, Multiple Sclerosis; NMO, Neuromyelitis Optica; RRMS, relapsing-remitting-MS; SPMS, secondary progressive-MS; PPMS, primary progressive-MS; RIS, radiologically isolated syndrome; VEP, visual evoked potential

11.1 Definition

Multiple Sclerosis (MS) is a chronic immune-mediated inflammatory condition of the central nervous system (CNS), characterized by demyelination and axonal degeneration.

11.2 Demographics

MS is among the commonest cause of neurological disability in young people with an annual incidence ranging from 2 to 10 cases/100,000 persons/year, a prevalence around 120 per 100,000. MS displays a north–south gradient, lower incidence being closer to the equator.

Clinically isolated syndrome (CIS) may be the first clinical presentation of MS. Three clinical MS courses are identified: relapsing-remitting (RR), secondary progressive (SP) and primary progressive (PP), which are described separately (Figs. 11.1 and 11.2).

11.3 Terminology

CIS – Acute or subacute first and single clinical event suggestive of an inflammatory demyelinating disease of the CNS. Typically, it involves a young adult and lasts at least 24 h, in absence of fever, infection or clinical aspects of diffuse encephalopathy.

The evolving definition of CIS related to the main question for the physician is whether the CIS is only an isolated episode or is the first episode of MS?

The definition of CIS has evolved in relation to progressive changes of criteria for MS diagnosis, mainly driven by the evolving relevance of MRI data to define the dissemination in space and time, and the characteristics that define the presence (or evolution) of a definite MS [1, 2].

Characterisations of CIS:

- CIS ‘pure’, consists of one symptom and one corresponding MRI alteration; CIS isolated in space (monofocal) and in time (monophasic),

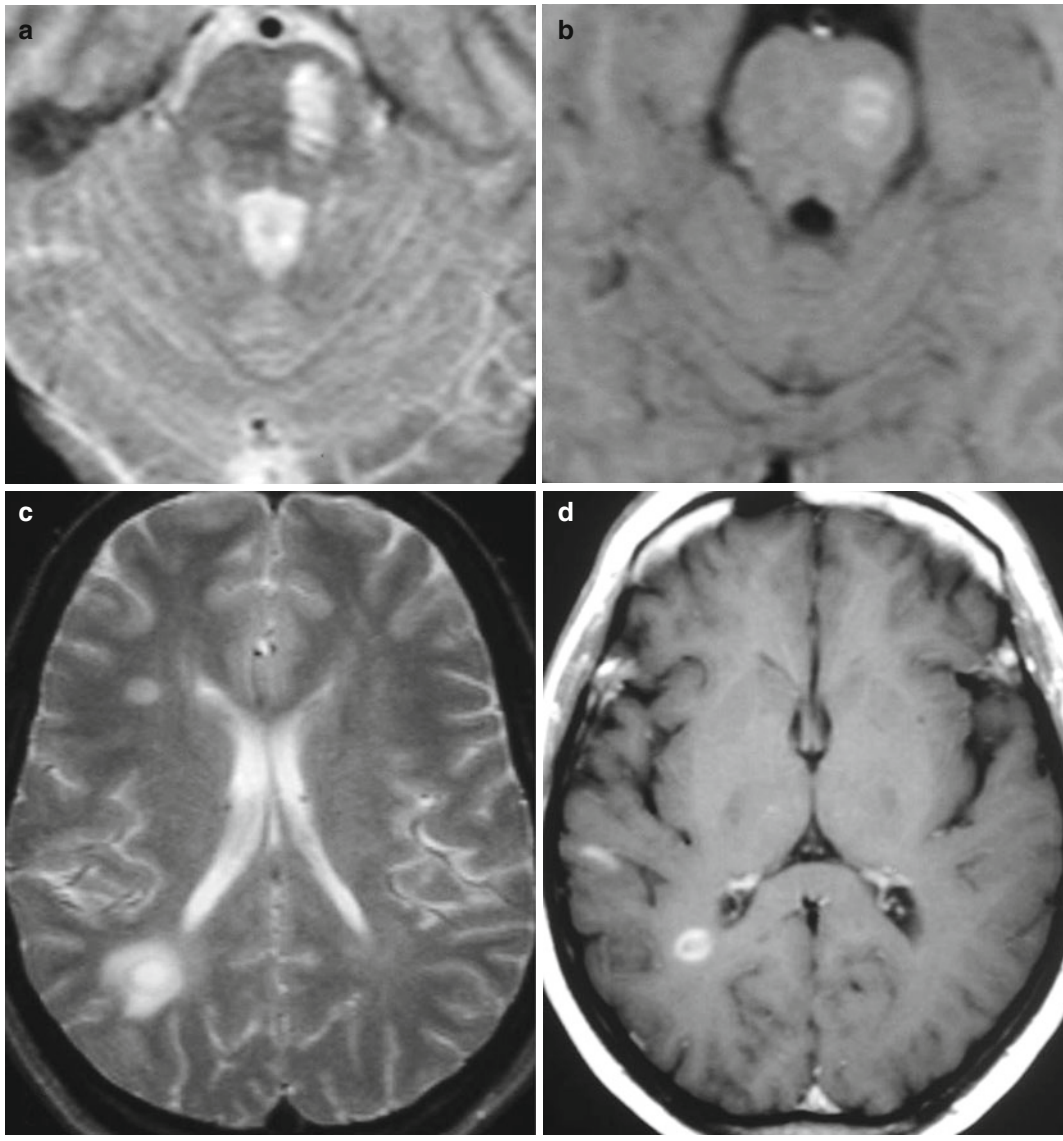

Fig. 11.1 MS, acute phase. T2-weighted image, (**a**, **c**) demonstrate focal hyperintensities in the left pons and in the white matter of the right hemisphere, respectively; note, edema around the plaque located in parietal region. After contrast medium administration, (**b**, **d**) enhancement is present in the active lesions

without dissemination in space or time of an underlying disease

- CIS with high probability of evolving into a clinically definite MS
  - Multifocal T2 abnormalities in the cerebral white matter (50–70 % of patients with CIS)
  - Multifocal onset
  - Inflammatory and immunological abnormalities in CSF
- Radiological isolated syndrome (RIS): presence of brain MRI features suggestive of a demyelinating disease with or without non-specific symptoms. Thirty-40 % of cases will show characteristics typical of CIS or MS within 5 years. Brain lesions should fulfil MRI criteria for MS with regard to number of lesions (more than 9), location (periventricular, juxtacortical, infratentorial) and gadolinium enhancement.

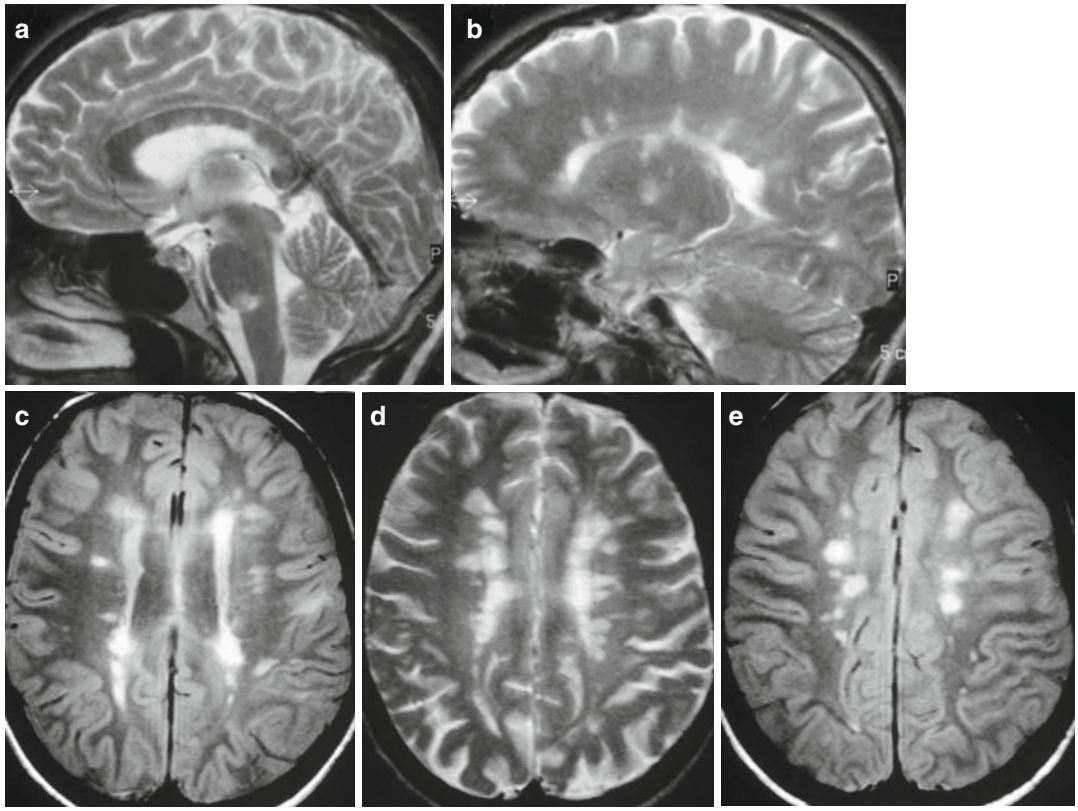

Fig. 11.2 MS, typical findings in different cases. Sagittal, (**a**, **b**) and axial, (**c**–**e**) T2-weighted images reveal typical numerous inflammatory demyelinating plaques located in the corpus callosum, in the brainstem, in the periventricular white matter and in perivenular spaces. Several lesions are confluent

- Demographics – Sex ratio: female/male: 2.5/1. Mean age at onset 30 years (20–40)

11.4 Clinical Features

- A clinical episode consistent with damage to white-matter tracts in young patients
- Data from large database: 21 % caused optic neuritis, 46 % long-tract symptoms and signs, 10 % brainstem syndromes and 23 % multifocal abnormalities

11.5 Diagnosis

11.5.1 Imaging

- One or more hyperintense lesions at T2-MRI
- Possible lesion enhancement in T1 with gadolinium
- Brain and spinal cord imaging
- Increased optic nerve volume in optic neuritis, with subsequent nerve atrophy (Fig. 11.3)

11.5.2 Laboratory

- CSF – oligoclonal bands in two-thirds of CIS
- Lack of a validated immunological marker to predict the development of MS

11.5.3 Top Differential Diagnosis

1. CIS in inflammatory demyelinating disease and MS.
2. MS: following the 2010 revision of McDonald criteria [1], MS can be diagnosed at the time of CIS, if other silent demyelinating lesion are found.

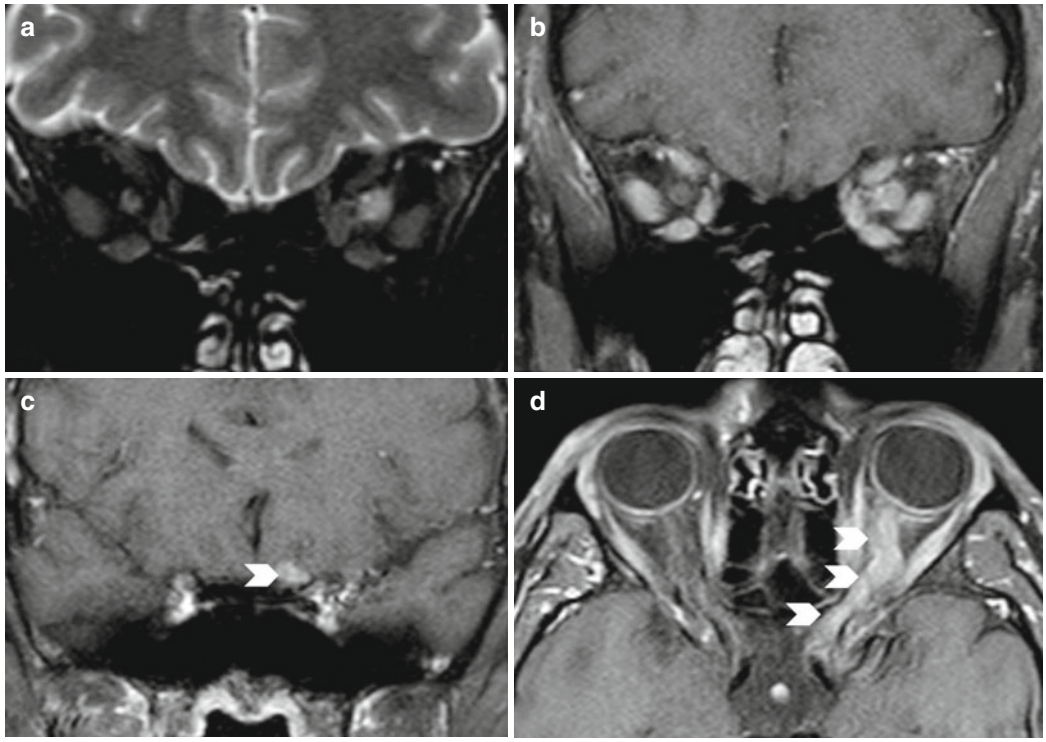

Fig. 11.3 NORB. Acute phase. Coronal T2-weighted image (**a**) shows enlargement and hyperintensity of the left optic nerve, and after contrast medium coronal image shows intense enhancement. (**b**) Enhancement of the intraorbital and intracranial left optic nerve is well documented in coronal and axial T1-weighted images after contrast medium (**c**, **d**) (*arrowheads*)

- CIS overlapping other diseases (neuromyelitis optica, neurosarcoidosis, LES vasculitis).

11.6 Principle of Treatment

11.6.1 Treatment of CIS [3]

- Many patients with CIS recover spontaneously.
- Intravenous steroids are often employed in cases with persistent symptoms (usually 3–5 day course of intravenous methylprednisolone with or without subsequent oral prednisone for 9–12 days). Steroids increase the speed and the amount of improvement in optic neuritis, the most studied variety of CIS.
- The efficacy of plasma exchange or intravenous immunoglobulin is controversial in CIS treatment.
- Immunomodulatory treatment for the prevention of MS:
  - Randomized, double-blind and placebo-controlled trials of interferon beta and glatiramer acetate in patients with CIS at risk of MS showed a delay in the development of clinically definite MS in the treated patients.
  - Immunomodulatory treatment is usually started a second clinical episode in most countries, but it could be prescribed in CIS at risk of MS.

11.7 Prognosis

11.7.1 Evolution to Definite MS [4]

- Presence of clinical or radiological dissemination in space and time.
- Probability of 17–45 % of a second episode in 2 years, about 50 % at 5 years, 60 % at 10 years and 68 % at 14 years. The median time to second episode is about 2 years.

11.7.2 Prognostic Factors for Evolution to MS

- Multiple lesions at first MRI evaluation (present in 50–70 % of CIS) with 50 % of conversion rate for optic neuritis and 90 % for other CIS in prolonged follow-up. In the cases of a unique lesion, the long-term risk of conversion to clinically definite MS is about 20 %. Both localization and number of lesions could be relevant for the risk of conversion, with infratentorial lesion at onset responsible for an increased risk.
- Younger age.
- Signs of inflammation in the CSF.
  - Raised cell count.
  - Oligoclonal bands (two or more oligoclonal bands in the CSF without corresponding bands in the serum).
- Multiple functional systems affected at onset.
- Other prognostic factors:
  - Cortical lesions at MRI
  - Atrophy of grey and white brain matter

11.7.3 Prognostic Factors for Long-Term Disability

- Spinal onset
- Polysymptomatic onset
- Efferent long pathways involvement at presentation
- Multiple lesions at first MRI evaluation
- Brain atrophy
- Incomplete remission of the clinical impairment after the first episode

11.8 Relapsing Remitting MS (RRMS)

11.8.1 Definition and Demographics

Relapsing Remitting (RRMS) is the most common MS phenotype involving around 85 % of patients. Clinical symptoms typically occur between 20 and 40 years of age. The frequency of MS has increased over the past century, mostly in women.

11.8.2 Clinical Features

Episodes of neurological impairment followed by complete or nearly complete recovery are typical of RRMS. In accordance with the different CNS regions involved, patients characteristically develop multiple functional problems such as visual and sensory disturbances, limb weakness, walking abnormalities, bladder and bowel symptoms and cognitive impairment.

- Clinical stages: RR-active is determined by clinical relapses and/or MRI activity (contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually). Periods of clinical stability between relapses define RR-not active [5]. In clinical trials different levels of severity have been used:
  - Active RRMS: defined by two clinical relapses in the previous 2 years. It is the most common clinical stage.
  - Highly active RRMS: defined by at least one relapse in the previous year while on therapy, and at least nine T2-hyperintensive lesions on brain magnetic resonance imaging (MRI) or at least one gadolinium-enhancing lesion.
  - Rapidly evolving severe RRMS: defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.

11.8.3 Diagnosis

MS is diagnosed according to the revised McDonald's criteria, which incorporate results of MRI [1]. The new diagnostic criteria include:

- Evidence of damage in at least two separate areas of the CNS

- The damage occurs at least 1 month apart
- Exclusion of other possible diagnoses

As a consequence, the diagnosis can be made earlier, at the first manifestation suggestive of MS (CIS), since the dissemination in space or time can be replaced by MRI findings even if clinical manifestations are absent. This has drastically changed the MS population included in clinical trials and clinical therapeutic decisions.

If the McDonald's criteria are fulfilled and there is no better explanation for the clinical syndrome, the diagnosis is 'MS'; if suspicious, but the criteria are not completely met, the diagnosis is 'possible MS'; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is 'not MS' [1].

Brain MRI detects dissemination of lesions both in space and time. At least three of four of the following MRI diagnostic criteria are required for the diagnosis of MS:

- One gadolinium-enhancing lesion or nine T2-hyperintense lesions in the absence of gadolinium-enhancement
- At least one infratentorial lesion
- At least one juxtacortical lesion
- At least three periventricular lesions

The ascertainment of dissemination in time by MRI requires a new T2 and/or gadolinium-enhancing lesion(s) at follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI, or simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time. Spinal cord MRI may be useful if brain MRI does not identify dissemination in space in a patient suspected of having MS.

- *CSF* – oligoclonal IgG bands different from those found in serum and/or elevated immunoglobulin G index (not specific of MS and not essential for its diagnosis). Mild pleocytosis. The additional value of CSF for MS diagnosis is still under discussion [1].
- *Neurophysiology* – Multimodal and, particularly, visual evoked potentials (VEP) may be abnormal.

11.8.4 Pathology

- The main pathological events in the CNS include focal lymphocytic infiltration and microglia activation followed by demyelination and axonal degeneration.

11.8.5 Top Differential Diagnoses

- Neuromyelitis optica (NMO) Acute disseminated encephalomyelitis (ADEM) (see Chap. 13).

11.8.6 Therapy

Relapses are treated with intravenous methylprednisolone 1 g daily for 3–5 days.

- Disease modifying drugs (DMDs): 11 DMDs are licensed for RRMS. Six of them are first-generation drugs (employed over the last 20 years): interferon beta-1a (Avonex and Rebif), interferon beta-1b, glatiramer acetate natalizumab and mitoxantrone (since 2000). Five new DMDs have been licensed over the last 5 years: fingolimod (since 2011), teriflunomide and alemtuzumab (since 2013), dimethyl fumarate and pegylated interferon beta-1a (since 2014).
- Off-label drugs: azathioprine is used in many countries; however, since the approval of interferons, it has not been recommended as a first line therapy for RRMS.
- Short-term efficacy of DMDs: natalizumab and interferon beta-1a (Rebif) are superior in the short-term to all other treatments for preventing clinical relapses (high quality evidence) and disability progression (moderate quality evidence) in RRMS (limited to 2–3 years' duration) compared to placebo [6]. Interferon beta-1b probably decreases the probability of relapses compared with placebo (moderate quality of evidence). The benefit–risk balance with azathioprine is uncertain; however, this agent might be effective in decreasing the risk of relapses

and disability progression over 2–3 years, compared with placebo. All these treatments may be associated with long-term adverse events. Interferon beta-1a, intravenous immunoglobulins and long-term steroids have an unfavourable benefit–risk balance in RRMS.

- There is uncertainty as to what extent the new DMDs vary in terms of efficacy and if they are superior to older ones. Uncertainty makes the 'cost' of their employment high and the plethora of available competing treatments makes therapeutic decision more difficult. Several of the new drugs are taken by mouth (generally the most convenient for MS patients). On the contrary, older drugs need to be injected, but efficacy and safety should guide therapeutic decisions.
- Long-term efficacy of DMDs: it is controversial [7, 8] and until now unknown. The lack of evidence about long treatment efficacy is caused by the substantial arguments regarding data analysis and interpretation in non-randomised studies. Recent results of a long-term follow-up study of interferon-β-1b demonstrated a significant reduction of mortality among treated patients [9].
- Pharmacological interventions for symptoms: fatigue, pain, spasticity, urinary symptoms, cognitive impairment and mood disorder require management.
- Non-pharmacological interventions for symptoms: exercise programmes, cognitive training and psychological interventions in a hospital or community setting should be tailored to meet the person's physical, cognitive or emotional symptoms.

11.8.7 Prognosis

MS has a chronic course evolving over 30–40 years. There are no reliable clinical or biological markers of disease progression and prognosis remains individually uncertain. Natural history studies suggest that about 30 % of patients with RRMS remain fully ambulatory without any treatment at 20 years from onset [10]. The development of a SP course is the major route to permanent long-term disability and it supervenes in about 80 % of RRMS by 20–25 years. After 15–18 years, about 50 % of patients need assistance to walk, are confined to wheelchair or bed or have died [11].

Mortality in patients with MS is significantly increased compared with the general population. MS is the main cause of death in more than 50 % of patients even if the incidence of deaths not due to MS varies among countries [9]. With the increasing incidence of MS, the improvement in care of the chronically disabled and different methodologies may explain the heterogeneity among study results.

The average life expectancy of MS patients is about 10 years shorter than for the general population. Patients older at onset or with a primary progressive course have shorter survival. Data on sex and mortality are contradictory.

Suicide is substantially increased in patients with MS, and, despite its varying incidence, mainly due to cultural reasons, it should be considered an MS-related cause of death.

11.8.7.1 Prognostic Factors

The prognostic value of early inflammatory relapses for late disability and progressive course remains uncertain [9, 11, 12]. Even among patients with frequent relapses (more than three) within the first 2 years of the disease, a large variability of long-term outcomes has been reported [9]. Natural history studies show that the principal determinant of long-term outcome is conversion to a progressive course, which is related to axonal loss and neurodegenerative processes [13]. The influence of early relapses might be exerted by shortening the latency to progression onset.

It is uncertain if younger age at onset suggests a favourable MS *course* [14, 15].

Cognitive impairment at baseline in patients with RRMS is prognostic of greater cognitive impairment over time, whereas high cognitive reserve is a positive prognostic factor for a milder disease course.

Age is a significant covariate for cognitive impairment in MS.

The prognostic value of MRI measures remains suboptimal [16].

No definite answer is available about the prospective of a better outcome granted by the presence of CSF oligoclonal bands [17].

11.9 Progressive Multiple Sclerosis

11.9.1 Terminology and Definition

Progressive Multiple Sclerosis is characterized by a progressive course, with continuous worsening of symptoms over time, with or without superimposed relapses. The clinical progression distinguishes progressive MS from the more common relapsing-remitting variants. Two main progressive forms are considered:

- *Secondary Progressive Multiple Sclerosis* (SPMS): natural history studies show that 50–80 % of untreated relapsing remitting multiple sclerosis (RRMS) develop a secondary progressive form after 10–30 years.
- *Primary Progressive Multiple Sclerosis* (PPMS): a less common clinical phenotype (10–15 % of MS patients) with an older age at onset (mean 40 years) and a progressive clinical course without any identifiable relapses.

11.9.2 Secondary Progressive Multiple Sclerosis (SPMS)

Key Facts	
• This form of the disease has an unfavourable prognosis and patients experience a slow worsening of their ability to functions, sometimes accompanied by fluctuations of the clinical picture.	• The prevalence of degenerative aspects strongly limits the efficacy of therapeutic approaches.

11.9.2.1 Diagnosis

- Clinical aspects: continuous worsening of disability over at least 6 months in a patient with RRMS
- *Imaging*
  - Average burden of brain T2-hyperintense lesions higher than in relapsing-remitting-MS
  - Load of spinal cord lesions higher than in relapsing-remitting-MS
  - Very rare gadolinium-enhancing lesions (superimposed relapses in 25–50 % of SPMS patients)
  - Load of brain T1-hypointense lesions as marker of neurodegeneration
  - Brain and spinal cord atrophy (correlated with neurological disability)
- *Laboratory*
  - Lack of laboratory markers for the transition from RRMS to SPMS and for the degree of progression in the SP course
- *Differential diagnosis*
  - Relapsing-remitting MS; primary progressive MS

11.9.2.2 Principle of Treatment of SPMS

Since inflammation plays a minor role in SPMS and neurodegenerative processes take place, the lack of drugs efficacious against neurodegeneration strongly limits the chance of preventive pharmacological approaches.

In SPMS, symptomatic and supportive treatments and coping strategies to improve the quality of life become major components of MS care.

- Treatment for superimposed clinical relapses.
  - Intravenous/oral/intramuscular corticosteroids are often utilized in case of persistent symptoms (see above).
- Disease prevention of inflammation and progression, 2 drugs approved for SPMS:

  - Interferon beta-1b, an immunomodulatory drug subcutaneously injected on alternate days. Randomized, double-blind studies showed a significant delay of progression in treated patients, with a positive effect on relapse rate and a better response in patients with higher prestudy inflammatory activity. Cochrane methodology applied to randomized placebo controlled trials confirmed that interferon beta-1b may reduce relapse risk but do not delay permanent disability.
  - Mitoxantrone has a proven effectiveness in clinical and radiological parameters, especially in the early phase of the progressive course, but with reports of life-threatening adverse events (leukemia and dose-dependent risk of cardiac toxicity).
- Symptomatic treatments of complications

11.9.2.3 Prognosis

The course of multiple sclerosis is largely unpredictable in the single patient due to the extensive individual variation in the course of the disease. Natural history studies of MS require a large number of patients and decades of follow-up and can encounter many potential sources of bias [15].

- *Prognostic factors*
  - Male sex and older age at onset: not statistically significant or negative factors in different series.
  - Presence of inflammatory relapses in SPMS course: not significant or positive factor.
  - Shorter time to progression: negative factor.
  - Magnetic resonance studies: brain atrophy and high lesion load are negative factor for long-term disability.
  - Multimodal evoked potential alterations are negative factors for clinical disability.
- *Worsening of disability:*
  - Disability scales in MS are weighted towards physical disability. Non-motor symptoms such as depression, fatigue and cognitive involvement are often underweighted.
  - Extended Disability Status Scale (EDSS) is the most commonly used disability scale; it is heavily weighted towards ambulation.
  - Progressive motor limitations are reported in a large number of studies, with progressive mean reduction of motor autonomy in SPMS patients over time:
    - 500 meters without rest within 2–10 years from the onset of SP course (EDSS 4)
    - 100 meters with unilateral support within 5–15 years (EDSS 6), mean age 55 years
    - Essentially restricted to bed/chair or in wheelchair in 15–25 years (EDSS 8), mean age 70 years
- *Role of cognitive involvement*
  - Frequent (40–75 %) and disabling symptom in SPMS
  - Primarily affects memory, sustained attention and information processing speed
- *Quality of life*
  - Severe progressive reduction of quality of life regarding:
    - Physical activity
    - Psychological aspects
    - Social interplay
- *Survival*
  - Few data in relation to difficulties in assessing time to death at different times and different geographic areas.
  - Median time to death: 35–50 years for SPMS patients.
  - Urinary tract infections, pneumonia/influenza, septic infection and pressure ulcer are more frequently reported in death of MS patients than in other populations.
  - Suicide: 2–5 % of death in SPMS.

11.9.3 Primary Progressive Multiple Sclerosis (PPMS)

Key Facts	
• 10–15 % of whole MS population. • Absence of a female predominance. • Onset of the disease about 10 years later than RRMS form, at a similar age of conversion to SPSM (mean 40 years). • Disease progression from onset characterized by continuous worsening with minor fluctuations without distinct relapses.	• SPMS and PPMS share many similarities and are considered as part of a disease spectrum modulated by genetic predisposition and environmental influences, and the differences between the two forms of the disease are quantitative rather than qualitative.

11.9.3.1 Diagnosis

- Spastic paraparesis being the typical clinical picture, the diagnosis of PPMS can commonly be a diagnosis of exclusion, and the passage of time is often a key element.
- According to the evolving criteria for diagnosis of PPMS, the 2010 revision of McDonald Criteria required 1 year of disease progression and at least two of the following:
  - Evidence for dissemination in space (DIS) in the brain magnetic resonance imaging (MRI)
  - Evidence for DIS in the spinal cord based on two or more T2 lesions in the cord
  - Positive cerebrospinal fluid (CSF): isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index

- *Clinical Features:*
  - A variable phenotype from progressive spastic paraparesis (83 % of cases), sphincter/sexual disfunctions (40 %) or sensory involvement (25 %) to a less common cerebellar dysfunction (10 % of cases) or hemiplegia (6 %)
  - High prevalence of corticospinal dysfunction, with weakness of pyramidal-type, hyper-reflexia and spastic increase in tone
  - Exercise-related weakness
  - Continuous worsening of disability from onset
  - Rate and character of the progressive phase similar in PPMS and SPMS
  - Common cognitive involvement, with impairments in attention, working memory, verbal memory, spatial reasoning and verbal fluency
- Imaging
  - MRI scanning of the spinal cord can be more informative than that of the brain.
  - Brain and spinal cord atrophy are more pronounced in PPMS than SPMS and RRMS; both gray and white matter are involved.
  - Higher load of spinal cord lesions is frequent in PPMS.
  - Very rare gadolinium-enhancing lesions (3 % of PPMS patients), more commonly seen early in the course of the disease.
  - Brain T1-hypointense lesions as common as in SPMS and considered a marker of neurodegeneration (black holes).
  - Diffuse mild hyperintensity is seen on T2-weighted images in about 50 % of PPMS patients.
  - Advanced techniques of MRI, such as diffusion tensor imaging (DTI) at spinal cord

level, showed a higher degree of alterations in PPMS than SPMS patients.
- *Laboratory*
  - Immunological positivity of cerebrospinal fluid (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index) is needed to make a definite diagnosis and is present in 80–90 % of PPMS cases. CSF cellular reaction is very uncommon in PPMS.
- *Top differential diagnosis* of spastic paraparesis
  - Cord compression (cervical spondylosis, tumours)
  - Hereditary leukodystrophies (hereditary spastic paraplegia etc.)
  - Metabolic and toxic (B12 deficiency etc.)
  - Inflammatory (CNS vasculitis etc.)
  - Infections (HTLV-1, HIV etc.)
  - Degenerative (motoneuron disease)
  - Vascular, paraneoplastic

11.9.3.2 Therapy

The (near) absence of relapses in PPMS patients interferes with the possible efficacy of immunomodulatory drugs that are effective mainly on the inflammatory aspects or RRMS and SPMS forms of multiple sclerosis. In this regard, at present there are no useful disease-modifying treatments for PPMS.

As in SPMS, also in PPMS symptomatic approaches and coping strategies to improve the quality of life become major components of MS care:
- Treatment for (very rare) superimposed clinical relapses.
  - Intravenous corticosteroids are often used in case of persistent symptoms (see above).
- Symptomatic treatments for complications.

11.9.3.3 Prognosis

Largely unpredictable due to the extensive individual variation in the course of the disease, the average rate of progression is similar for PPMS and SPMS, and long periods of relative stability have been reported.

High variability in disability accrual:
- 25 % of patients require assistance to walk at 7 years from onset.
- 25 % of patients could walk independently 25 years after onset.

High variability in brain atrophy progression between patients with a certain persistence of progression rate curve within individuals [18].

Prognostic Factors
- Cervical cord atrophy correlates with disability.
- Decrease in cord area and increase of invalidity over time are correlated.
- Corpus callosum damage predicts disability and cognitive dysfunction after 5 years.
- Disease duration, brain volume and poor walking ability at baseline are predictors of clinical outcome at 5 and 10 years.
- Early brain grey matter atrophy: negative prognostic factor.
- The involvement of three or more neurological systems are considered adverse prognostic factors.
- Gender, age and mode of onset are not prognostic indicators.

Survival
- Median time to death: 33 years in PPMS patients.
- Causes of death: 45–55 % of deaths were directly attributable to MS.
- Urinary tract infections, pneumonia/influenza, septic infection and pressure ulcer are more frequently reported in death of MS patients than in other populations.
- Suicide: <3 % of death in PPMS

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Myelin Disorders: Devic's Syndrome

12

Graziella Filippini

Key Facts

- **Terminology and definition** – Neuromyelitis optica is an immune-mediated condition of the CNS that preferentially involves the spinal cord and the optic nerves.
- **Clinical features** – Severe episodes of recurrent optic neuritis and myelitis. Brain involvement is present in most cases.
- **Diagnostic markers**
  - **Blood** – Serum autoantibodies targeting aquaporin-4.
  - **CSF** – Oligoclonal bands or elevated IgG index in 10–20 % of patients.
  - **MRI** – Spinal cord lesions longer than three spinal segments and primarily involving the central part of the spinal cord, optic nerve neuritis.
  - **Neurophysiology** – Reduced amplitudes and/or prolonged latencies of VEP.
- **Top differential diagnoses** – MS; myelitis and/or optic neuritis of various origins (e.g., systemic lupus erythematosus, Sjögren's syndrome, sarcoidosis, vasculitis).
- **Prognosis**
  - **Principle of treatment** – Corticosteroids; plasma exchange; long-term immunosuppression; symptomatic treatments.
  - **Disability** – Most patients with AQP4-IgG positive NMO/NMOSD have a severe, relapsing course. Within 5 years from onset, more than 50 % of patients with relapsing NMO are blind in one or both eyes or need assistance to walk or are confined to wheelchair. Patients with negative AQP4-IgG NMO or NMOSD often have a less severe course.

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Abbreviations

AQP4-IgG, Aquaporin-4 autoantibodies; CNS, Central nervous system; CSF, Cerebrospinal fluid; LETM, Longitudinally extensive transverse myelitis; NMOSD(s), NMO spectrum disorder(s); GFAP, Glial fibrillary acid protein; MOG, Myelin oligodendrocyte glycoprotein; MRI, Magnetic resonance imaging; MS, Multiple Sclerosis; NMO, Neuromyelitis Optica; ON, Optic neuritis; SLE, Systemic lupus erythematosus; VEP, Visual evoked potential

12.1 Definition

Neuromyelitis optica NMO (synonyms: Devic's syndrome, NMO spectrum disorders (NMOSDs); optic neuritis (ON); longitudinally extensive transverse myelitis (LETM); opticospinal syndrome) is an immune-mediated inflammatory disorder of the central nervous system (CNS) that preferentially involves the spinal cord and the optic nerves. It is characterized by primary damage to astrocytes caused by aquaporin-4 (AQP4-IgG) autoantibodies leading to secondary demyelination and axonal injury. Detection of AQP4 in serum has prompted recognition of a heterogeneous spectrum of clinical disorders (NMOSD) that previously would not have met diagnostic criteria for NMO.

12.2 Demographics

NMO is a rare condition; knowledge regarding its epidemiology is limited. Its incidence is 0.53–4/1,000,000 population; prevalence is 5.2–40.4/1,000,000 in Europe and North America. Clinical symptoms more often occur between 35 and 45 years of age, but NMO may also occur in children and the elderly. AQP4 antibodies are more frequent in women.

NMO is sporadic, though 3 % of familial cases have been reported. African-Americans with demyelinating disease commonly have an aggressive optic-spinal syndrome.

12.3 Clinical Features

In most cases (80–90 %) NMO is a relapsing condition with severe attacks of LETM or unilateral or bilateral optic neuritis (ON), often causing loss of vision with incomplete recovery. A monophasic course is less frequent (10–20 % of cases) and is more often associated with simultaneous optic neuritis and myelitis. Brain involvement, as initial event or at relapse [1], is recognized and included among the diagnostic criteria for NMO/NMOSD [2]. Brain damage is present in more than 60 % of patients; hypothalamus, medulla, and brainstem are most frequently involved [3]. Syndromes of inappropriate *antidiuretic hormone* secretion (SIADH) or cognitive impairment have been reported [4].

12.4 Diagnosis

NMO is diagnosed according to the revised criteria for "definite" NMO [2], which recommend the presence of optic neuritis, acute myelitis, and at least two of three diagnostic tests, i.e., a contiguous spinal cord MRI lesion at least three segments in length, brain MRI at onset "non-diagnostic" for MS, or anti-AQP4-IgG seropositivity. AQP4-IgG positive LETM is classified as neuromyelitis optica spectrum disorder (NMOSD) [1, 2].

- *Serum* – Autoantibodies against aquaporin-4 (AQP4-IgG) have specificity for NMO/NMOSD greater than 90 %, but sensitivity ranges from 50 to 70 %. Assays detecting IgG binding to cells expressing recombinant AQP4 with quantitative flow cytometry or visual observation are more sensitive than ELISA and immunoprecipitation [5]. More than half of the patients with NMOSD are AQP4-IgG positive. A proportion of 10–30 % of NMOSD patients remains AQP4-IgG antibody-negative during acute attacks. Retesting is warranted in high-risk patients.

  Autoantibodies anti-myelin oligodendrocyte glycoprotein (MOG) have been reported in

patients with AQP4-IgG seronegative NMOSD [6]; however, their pathogenic, diagnostic, prognostic, and therapeutic relevance remains unclear.

CSF – White cell counts may be normal or only mildly elevated, but cell counts >100/μl are possible. An elevated albumin CSF/serum ratio and an increase in total protein are present in approximately 50 % of cases. CSF lactate levels may be increased during acute myelitis in 40 % of cases [4].

MRI – Spinal cord lesions longer than three segments (LETM) often with contrast enhancement and primarily involving the central part of the spinal cord are found [2]. However, short transverse myelitis is not uncommon. Lesions are preferentially located at the diencephalon, hypothalamus, aqueduct and brainstem, which are sites of high AQP4 expression [3]. Cortical atrophy, mainly in the visual cortex, and contrast enhancement may be present.

- *Magnetic resonance spectroscopy* and diffusion tensor imaging may be useful to distinguish NMO from multiple sclerosis (MS).
- *Neurophysiology* – Visual evoked potentials (VEP) show reduced amplitudes and/or prolonged latencies.

12.5 Pathology

AQP4-IgG autoantibodies are pathogenic [1]. The main neuropathological features in the CNS include AQP4 loss or decrease in active demyelinating lesions, with dystrophic astrocytes, and perivascular inflammatory infiltrates. Myelin and tissue vacuolation, macrophages containing glial fibrillary acid protein (GFAP) positive debris, complement activation, and blood vessel thickening are also found.

12.6 Top Differential Diagnoses

- Multiple sclerosis; optic neuropathy and myelitis of different origin.
- Brain involvement in NMO may be less frequent than in MS at onset [3]. Patients with NMO may worsen when treated with immunomodulatory agents employed in MS [7, 8].

12.7 Prognosis

12.7.1 Principle of Treatment

- Corticosteroids and plasma exchange are useful for management of acute attacks.
- Randomized controlled trials of immunosuppressive therapies for NMO/NMOSD are not available in the literature and there is no consensus on how to select initial therapy.
- Non-randomized studies have suggested that initial treatment with rituximab, mycophenolate, and, to a lesser degree, azathioprine significantly reduces relapse rates in NMO and NMOSD patients. Patients for whom initial treatment fails may achieve remission if switched to another useful drug.
- Immunosuppressant therapy reduces the relapse rate in both AQP4-IgG–positive and AQP4-IgG–negative patients with relapsing LETM [5].
- Disease-modifying drugs used for MS worsen NMO/NMOSD and may cause blindness, paraplegia, and other permanent disabilities [7, 8, 9].

12.7.2 Prognosis

Most patients with AQP4-IgG positive NMO/NMOSD have a generally severe, frequently relapsing clinical course. A monophasic course is rare and is more often associated with simultaneous ON and myelitis [10]. A secondary progressive worsening of disability is unusual [1]. Recovery from relapses is usually incomplete, and disability worsens in most patients with relapses.

Within 5 years of disease onset, more than 50 % of patients with relapsing NMO are blind in one or both eyes, need assistance to walk, or are confined to wheelchair [10]. Likely outcome has

improved as AQP4-IgG detection makes early diagnosis easier and immunotherapy timely, but outcome results on large cohorts are not available in the literature.

AQP4-IgG–positive patients with recurrent LETM, like those with recurrent LETM-onset NMO, have a worse motor outcome than the entire AQP4-IgG–positive NMO cohort [5].

Patients with negative AQP4-IgG NMO or NMOSD usually have a less severe course than AQP4-IgG positive patients, but their prognosis remains uncertain because of the clinical heterogeneity of these groups [6].

Prognostic Factors [11]

- Nonwhite race/ethnicity is a significant predictor of NMOSD risk.
- Longer inter-attack interval between the first two relapses, older age at onset, female sex, and less severe motor impairment at beginning of myelitis are predictors of a relapsing course.
- A history of other autoimmune diseases, higher relapse frequency in the first 2 years of disease, and the severity of the first relapse are predictors of a worse prognosis and are associated with mortality due to relapsing NMO.
- AQP4-IgG seropositivity predicts relapse or conversion to NMO and poor visual outcome in patients with recurrent optic neuritis [12].
- AQP4 seropositivity predicts recurrence or conversion to NMO in patients with single attack of LETM [5].

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Myelin Disorders: Postinfectious Neurological Syndromes

13

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Abbreviations

ADEM, Acute disseminated encephalomyelitis; CNS, Central nervous system; E, Encephalitis; EM, Encephalomyelitis; Ig, Immunoglobulin (Ig); IVIG/IVIg, Intravenous immunoglobulin; PINS, Postinfectious neurologic syndrome; PNS, Peripheral nervous system

Postinfectious neurologic syndromes (PINSs) of the central nervous system (CNS) include disorders, sometimes relapsing, triggered by an antigenic challenge, such as a systemic infection or a vaccination. They differ from acute CNS infections because they lack specific biological markers, are not due to direct infections of the neural tissue, and are predominantly inflammatory and demyelinating [1].

The umbrella term "PINS" includes syndromes that are heterogeneous with respect to clinical presentation, severity, dissemination of lesions, and disease course [2]. Each of these variables may affect the prognosis.

CNS involvement may be "disseminated," such as in the classic acute disseminated encephalomyelitis (ADEM), or site-restricted, such as in isolated encephalitis and myelitis. Some forms are complicated by additional peripheral involvement [3].

The disease course is usually monophasic, but relapses may occur, commonly without the need of a further antigenic trigger.

Although rare, PINS can be severe or fatal, and patients may require intensive care unit (ICU) admission because of tetraplegia, seizures, or coma, and may be associated with severe residual disability.

A comprehensive systematic assessment of disability and prognostic predictors is difficult, due to the rarity of PINS; the small reported series usually do not include the full spectrum of their clinical variants; moreover, most studies are retrospective and have a short follow-up. Candidate prognostic predictors include age, delay in diagnosis, extent of cerebrospinal fluid (CSF) inflammatory reaction, MRI abnormalities, response to treatment, and disease course.

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Key Facts

- **Definition** – Inflammatory CNS or CNS + peripheral nervous system (PNS) syndrome complicating infections/vaccinations.
- **Clinical features** – Acute/subacute onset of polyfocal neurological signs and/or encephalopathy, often with concomitant fever and meningeal signs.
- **Diagnostic markers**
  - **Laboratory** – Exclusion of direct infections; raised CSF proteins/cells.
  - **Imaging** – *Brain* – multifocal contemporary lesions, white > gray matter, ± enhancing. *Spinal cord*: multifocal or longitudinally extensive lesions, ± root enhancement.
  - **Neurophysiology** – Polyradiculoneuritis in 30 %.
- **Top differential diagnosis**
  - CNS infections.
  - Multiple sclerosis.
  - Systemic autoimmunities.
  - Neuromyelitis optica and other CNS diseases associated with specific autoantibodies.
- **Principles of treatment** – High-dose steroids effective in 60 % of cases; forms with peripheral involvement may benefit from IVIg.
- **Prognosis**
  - **Survival** – >95 %.
  - **Disability** – Residual motor disability in 50 % of cases, considering all variants; poorer prognosis if isolated myelitis, PNS involvement, older age, higher CSF inflammation, hyperacute onset.
  - **Disease course** – Usually monophasic; relapsing in 20–30 % of cases, either at the same site ("recurrent PINS") or at a different site ("multiphasic PINS").

13.1 Variants

According to the distribution of lesions within the CNS and the PNS, there are five possible clinical variants of PINS:

1. *Postinfectious encephalomyelitis*, classically labelled as *ADEM*, is the best-known form, characterized by widespread involvement of both the brain and the spinal cord.
2. *Postinfectious encephalitis.*
3. *Postinfectious myelitis*, which represent site-restricted forms.
4. *Postinfectious encephalomyeloradiculoneritis.*
5. *Myeloradiculoneuritis*, when the above conditions are complicated by PNS involvement.

13.2 Causative Agent

An infection (50–80 %) or, less commonly, a vaccination (10 %) precedes the neurological onset by 1–30 days. The most common antecedent is a benign upper respiratory infection, usually viral.

PINSs with a known etiology account for 10–30 % of the total. Over 30 different infectious agents have been identified as triggers.

13.3 Epidemiology

Age: children more often than adults, but can occur at any age.

Sex: no sex predominance.

The incidence of PINSs is about 0.8/100,000/year. The exact epidemiology of the different disease variants is unknown.

PINSs are rare, yet the most common postinfectious disorders.

They are most common in winter and spring, in line with the spreading of the infectious triggers.

13.4 Clinical Features

The neurological deficits are acute/subacute in onset, reaching their maximum within hours to a few days, and are usually preceded or accompanied by fever. Signs and symptoms

depend on the systems involved; however, they are polyfocal.

Encephalitis includes one or more of the following: polyfocal brain signs (aphasia, motor/sensory involvement), ataxia, optic neuritis, consciousness alteration, and seizures in 10–35 % of patients.

Myelitis although recognized as site-restricted variants, the picture is, however, polyfocal, including motor and sensory and urinary dysfunction.

Peripheral involvement occurs in up to one third of cases.

As a general rule, seizures, meningeal signs, and encephalopathy prevail in childhood series (often mimicking infective encephalitis), while in adults and elderly populations a variety of focal deficits, often with spinal cord and peripheral involvement, are more common.

13.5 Diagnostic Markers

Specific markers are not available: the diagnosis is based on a combination of clinical and radiological features and exclusion of other acute encephalopathies/myelopathies [2, 4].

13.6 Clinical Features

Acute/subacute onset; antecedent infection/vaccination <30 days; no history suggestive of an earlier demyelinating episode.

13.6.1 Laboratory

CSF Usually no CSF oligoclonal bands; lympho-monocytosis up to 1000/mm^3; elevated albumin; normal IgG index.

MR Brain: multifocal, hyperintense lesions on T2/FLAIR images, ± enhancement, predominantly of the white matter.

Spinal cord Multifocal or monofocal longitudinal lesions, mainly involving the central gray matter. Root enhancement may be seen.

13.6.2 Neurophysiology

Neurophysiological investigations should be performed, in view of their prognostic implications.

Diagnostic criteria, unavailable for adults, were formulated for the pediatric population in 2007: (1) polysymptomatic onset with encephalopathy; (2) evolution over a period from 1 week to 3 months, with subsequent improvement or recovery; and (3) MRI: acute lesions which are mainly symptomatic [5].

13.7 Differential Diagnosis

- Direct CNS infections
  - Positive CSF culture or serum and CSF IgM antibodies
- Metabolic and toxic diseases
- Systemic autoimmune disorders
- CNS inflammatory diseases associated with specific antibody markers:
  - Positive anti-AQP4 and anti-GQ1b antibodies
- Multiple Sclerosis:
  - Previous diagnosis of an inflammatory CNS disease/isolated optic neuritis
  - MR: periventricular white matter; lesions of different ages; development of new MR lesions, even asymptomatic, during a 2-year follow-up

13.8 Pathology

Perivenular inflammation, edema, and demyelination. Lymphocytic infiltrates. Lesions are of similar histological age. Relative axonal and arterial preservation.

13.9 Pathogenesis

The involvement of the immune system is thought to imply the molecular mimicry phenomenon.

13.10 Principles of Treatment

Initial treatment: high-dose steroids effective in 50–80 % of patients.

Steroid-refractory cases: (a) plasma exchange; (b) IVIG, 0.4 mg/kg in 5 days. IVIG have been proven effective in patients showing both CNS and PNS involvement.

It is advisable to avoid immunization for at least 6 months after the diagnosis of PINS, as relapses have occurred following routine vaccinations.

13.10.1 Prognosis

13.10.1.1 Disease Course and Relapses

PINSs are usually monophasic, but relapses are described and increasingly reported [2, 4]. Based on the known time frame of relapses, a 2-year follow-up should be adopted to assess the disease course and the outcome (Fig. 13.1).

Relapses occur after a clear-cut time of neurological stabilization and should not be confused with "rebounds" or "pseudo-relapses": the latter are neurological fluctuations due to reactivation of the same lesions, related to steroid discontinuation, typically occurring within 1–3 months from disease onset.

Relapses are classified as follows:

- Recurrent-PINS, when the new event is a recurrence of the initial symptoms, with or without imaging enlargement or new enhancement of the original lesion, and no new MRI lesions.
- Multiphasic-PINS, when the new event affects different anatomic areas; MRI must show new areas of involvement, but also demonstrate complete or partial resolution of those lesions associated with the first event.
- In Pediatric criteria, the occurrence of a multiphasic course is accepted for disseminated forms only, and provided that, again, the onset is polysymptomatic with encephalopathy.
- The frequency of relapses is 10–30 %, with recurrent forms >>> than multiphasic; variants with peripheral involvement have a higher risk of relapses.

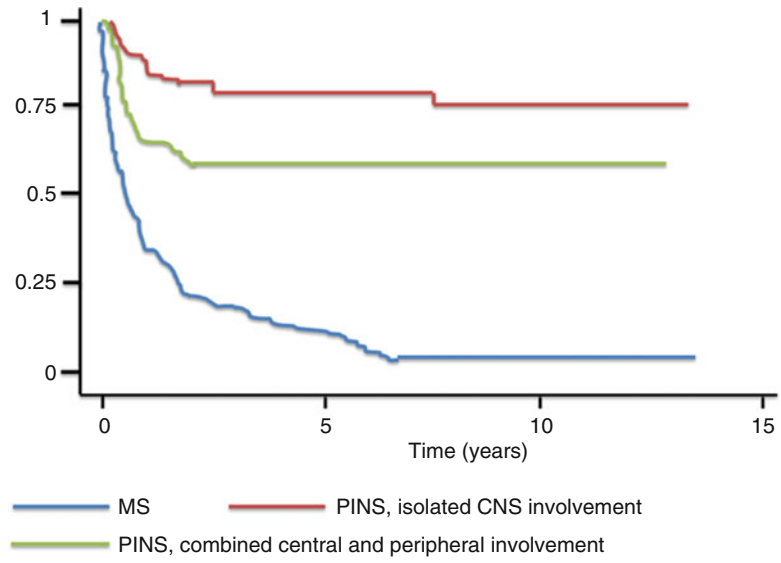

Fig. 13.1 Relapse-free survival in PINSs and in MS: patients with PINSs, either those with isolated central damage (encephalitis, encephalomyelitis, and myelitis, *red line*) and the variants with additional peripheral involvement (encephalomyeloradiculitis and myeloradiculitis, *green line*), show a lower risk of relapses compared to multiple sclerosis (*blue line*); moreover, relapses in PINSs have a peculiar timeframe, occurring within the first 2 years from onset. Among PINS, forms with peripheral damage show a higher rate of relapses compared to pure central syndromes

13.10.2 Mortality and Disability

While historical groups showed mortality rates reaching 30 %, mortality rate is <5 % in recent series, probably due to improved early recognition of the disease, treatment with steroids, and change in supportive care. Thus, despite the severity characterizing the acute phase, the mortality rate is relatively low. Causes of death include sepsis and pneumonia; but among those directly related to PINS, there is respiratory failure due to brainstem involvement, raised intracranial pressure, uncontrolled seizures, and cardiovascular autonomic dysfunction.

13.10.2.1 Disability

A high proportion of residual disability occurs.

The average time to recovery ranges from 1 to 6 months, although full recovery or stabilization of deficits may occur for up to 2 years, especially in variants with spinal cord or peripheral involvement.

The spectrum of recovery spreads from childhood encephalomyelitis and encephalitis, with complete recovery in 80–90 % of cases, to adult/elderly transverse myelitis and myeloradiculoneuritis, which shows the worst outcome, not only in terms of residual disability (severe in 60 %), but also for steroid resistance (60 %) and risk of relapse (40 %).

Independent of the clinical form (with or without myelitis or peripheral involvement), the outcome is worse for adults than for childhood series with respect to hospitalization, ICU admissions, and recovery. Both in children and adults, isolated myelitis are accompanied by more severe outcomes compared to myelitis occurring in the context of encephalomyelitis; again, myelitis have better outcome in children compared to adults (Table 13.1) (however, during the acute phase, the neurological dysfunction may be more severe in children).

The most common residual deficits are as follow.

- Childhood:
  - Focal motor deficits, visual problems, and epilepsy. Behavioral and subtle neurocognitive deficits (mainly involving attention

Table 13.1 Main outcome parameters in childhood and adult series, divided in three main PINS forms: encephalomyelitis, myelitis, and forms complicated by peripheral involvement

	Mortality	Sequelae	Steroid resistance	Relapses
Pediatric encephalomyelitis	1.3 % (0–4 %)	80 % complete recovery or final EDSS <1 19 % motor dysfunction or unspecified, severe 29 % cognitive and learning dysfunction, usually mild	10 % (0–22 %)	14 % (0–28 %)
Adult encephalomyelitis	3 %	50 % complete recovery 30 % poor outcome	20 %	25 %
Mixed adult and pediatric encephalomyelitis, with comparison	0.3 % pediatrics 12 % adults	Residual deficits in 12.5 % pediatrics 25 % adults	–	–
Pediatric postinfectious myelitis	4 %	44 % motor dysfunction 80 % urinary dysfunction	40 %	8 %
Adult postinfectious myelitis	0.5 %	30 % good outcome 30 % fair outcome (ambulatory but with spasticity, urinary dysfunction, sensory signs) 40 % poor outcome (completely or largely unable to walk, severe urinary dysfunction)	30 %	40 %
Forms complicated by PNS involvement	1 %	30 % good outcome, but recovery is usually delayed 70 % poor outcome	65 %	40 %

and executive functions) have been identified in up to 30 % of patients on long-term follow-up, with higher risk in patients with a younger age of onset (<5 years).

- Adults:
  - Focal deficits, mainly motor, bladder dysfunction and ataxia. Myelitis is followed by often permanent urinary dysfunction in up to 80 % of cases.

As a whole, predictors of poor prognosis in PINS are:

- Older age, both for children and adults
- Severity of neurological dysfunction at onset (consciousness impairment and seizures, severe motor weakness and urinary dysfunction)
- Higher CSF albumin
- Absence of fever at onset
- Spinal cord involvement
- Peripheral involvement

Controversial prognostic predictors are: sex, extent and site of MRI lesions, CSF cells, and delay in diagnosis.

Poor response to steroids should not be considered as a poor prognostic factor, since it does not exclude a better response to other immune treatments [1, 2, 4, 6].

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Leukodystrophies

14

Ettore Salsano and Davide Pareyson

Key Facts

- **Terminology and definition** – Leukodystrophies are a highly heterogeneous group of *hereditary* diseases *primarily* affecting the white matter of the central nervous system (CNS).
- **Clinical features** – Onset of the adult forms ≥16 years. Each disease is rare or very rare (prevalence ≤5 in 100,000). Clinical manifestations are highly variable: walking difficulties, spasticity and/or ataxia, behavioral and cognitive decline, and sphincter disturbances. Asymptomatic cases can be identified.
- **Diagnostic markers**
  - **Imaging (MRI)** – Brain white matter abnormalities on T2-weighted and FLAIR sequences. Spinal cord MRI can be occasionally useful.
  - **Laboratory** – Genetic analyses and, in some cases, biochemical investigations definitely confirm the diagnosis. Routine CSF analysis is unremarkable.
  - **Neurophysiology** – Nerve conduction studies can reveal peripheral nerve involvement mostly in the hereditary metabolic leukodystrophies.
- **Top differential diagnoses** – Acquired diseases of the brain white matter: Multiple sclerosis, infectious diseases (e.g., acquired immunodeficiency syndrome, progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis); toxic leukoencephalopathies; posterior reversible encephalopathy syndrome (PRES); cerebral amyloid angiopathy (CAA) and CAA-related inflammation; Langerhans and non-Langerhans cell histiocytosis; gliomatosis and lymphomatosis cerebri; inherited diseases (e.g., cerebral autosomal dominant arteriopathy with stroke and ischemic leukoencephalopathy [CADASIL], Fabry's disease, organic acidurias, mitochondrial disorders).
- **Therapy** – There is no disease-modifying therapy except for a very few diseases treated with hematopoietic stem cell transplantation with or without gene therapy.
- **Prognosis** – Adult-onset leukodystrophies are characterized by relentless progression. The prognosis of the leukodystrophies presenting in adulthood is typically better than the prognosis of those with onset in infancy or childhood.

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Abbreviations

ADLD, Autosomal dominant leukodystrophy; AMN, Adrenomyeloneuropathy; AO, Adult onset; APBD, Adult polyglucosan body disease; ARSA, Arylsulfatase A; AxD, Alexander Disease; c-ALD, Cerebral form of X-ALD; CAA, Cerebral amyloid angiopathy; CSF1R, Colony stimulating factor 1 receptor; FLAIR, Fluid attenuated inversion recovery; FXTAS, Fragile X-associated tremor/ataxia syndrome; GALC, Galactosylceramidase; GFAP, Glial fibrillary acidic protein; HSCT, Hematopoietic stem cell transplantation; HDLS, Hereditary diffuse leukoencephalopathy with spheroids; LMNB1, Lamin B1; LBSL, Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; LKPAT, Leukoencephalopathy with ataxia; LVWM, Leukodystrophy with vanishing white matter; MLD, Metachromatic leukodystrophy; NALD, Neuroaxonal leukodystrophy; NHD, Nasu-Hakola disease; PMD, Pelizaeus-Merzbacher disease; PMLD1, Pelizaeus-Merzbacher-like Disease type 1; RIL, Radiologically isolated leukoencephalopathy; X-ALD, X-linked adrenoleukodystrophy.

14.1 Definition

Leukodystrophies (Greek: leukós [λευκός], "white", and "dýstrophos" [δύστροφος], "hard to rear") are a highly heterogeneous group of hereditary diseases primarily affecting the white matter of the central nervous system (CNS). On brain MRI, they are typically characterized by symmetric, variably extensive, mild-to-prominent T2-hyperintensity of the affected white matter. The diagnosis of leukodystrophies *in vivo* is not based on clinical assessment but relies on neuroimaging studies. However, some "classical" leukodystrophies, such as X-linked adrenoleukodystrophy (X-ALD) or Pelizaeus-Merzbacher disease (PMD), can present without white matter changes on brain MRI and there is a growing number of hereditary diseases with white matter changes on brain MRI resembling a leukodystrophy (e.g., spastic paraplegia 11 (SPG11), SPG35, and fragile X-associated tremor/ataxia syndrome [FXTAS]). These forms are conventionally included in other disease groups and/or their neuropathology and physiopathology are unknown or not sufficiently known to support their inclusion in the leukodystrophy group. Consequently, many hereditary diseases can or cannot be arbitrarily included under the chapter of leukodystrophies [1–3].

Here, we have covered the prognosis of the adult-onset (age ≥16 years) forms of the "classical" metabolic leukodystrophies, i.e., X-ALD (Fig. 14.1), metachromatic leukodystrophy (MLD), and Krabbe disease. We have also reviewed the prognosis of a series of "new" leukodystrophies with typical infantile or childhood onset, such as leukodystrophy with vanishing white matter (Fig. 14.2), and Alexander Disease (AxD) (Fig. 14.3), because they can also present in the adulthood. Finally, we have briefly discussed the novel *CLCN2*-related leukoencephalopathy with ataxia (LKPAT) and what we have called "radiologically isolated leukoencephalopathies" (RILs) (Table 14.1). In contrast, we have not addressed very rare hereditary metabolic diseases, such as 3-methylglutaconic aciduria, L-2-hydroxyglutaric aciduria, and methylmalonic aciduria with homocystinuria, despite the fact that they can present in adulthood as leukodystrophies (see Chap. 19). Similarly, we have excluded the hereditary leukoencephalopathies which are associated with cerebral microangiopathies.

There are few studies addressing the prognosis of adult-onset leukodystrophies, mainly because of their rarity. In general, the prognosis of the leukodystrophies presenting in adulthood seems to be better than for those with onset in infancy or childhood. Notwithstanding, their natural history is commonly characterized by relentless progression, and no disease-modifying therapy has been proved to be effective for the majority of them. Hematopoietic stem cell transplantation (HSCT) with or without gene therapy, however, is a promising treatment for some of them, and supportive care has improved the quality of life and prolonged the survival of most of the affected subjects.

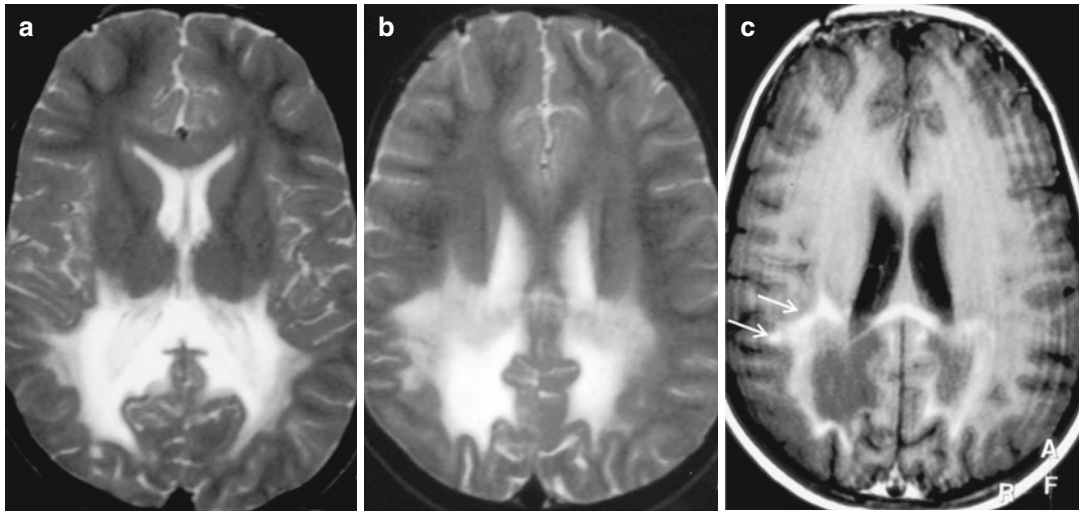

Fig. 14.1 Cerebral form of X-linked adrenoleukodystrophy, c-ALD. MRI axial T2-weighted images (**a**, **b**) show marked bilateral symmetrical hyperintensity in the splenium of the corpus callosum and in the adjacent white matter. Post-contrast image (**c**) shows symmetrical linear peripheral contrast enhancement in the corresponding areas (*arrows*).

14.2 Adrenoleukodystrophy (X-ALD)

Definition and epidemiology Adrenoleukodystrophy (X-ALD) is an X-linked metabolic disease caused by mutations in the *ABCD1* gene, and is the most common inherited leukoencephalopathy, with an estimated prevalence of hemizygotes (i.e., males) plus heterozygotes (i.e., females) of 1:16,800 in the USA.

Clinical features The penetrance in males seems to be approximately 90 % [4], whereas X-ALD female carriers can develop neurological symptoms in 20–50 % of cases, usually in the fourth or fifth decade of life [5, 6]. In males, X-ALD encompasses a wide spectrum of forms with varying severity, ranging from the most severe cerebral form (c-ALD) – characterized by behavioral and cognitive decline as predominant manifestations – to the less severe adrenomyeloneuropathy (AMN) – characterized by spastic paraplegia, lower limb sensory disturbances, sphincter dysfunction and impotence as predominant manifestations – or even to adrenal failure-only phenotype. There is no genotype-phenotype correlation, and the same mutation can lead to different forms even within the same family.

Therapy Lorenzo's oil is not useful for c-ALD, whereas its efficacy for adrenomyeloneuropathy (AMN) remains uncertain because of a lack of randomized placebo-controlled studies in adulthood [7]. Heterologous hematopoietic stem cell transplantation (HSCT) from HLA-matched donor and autologous HSCT with gene therapy (i.e., lentiviral hematopoietic stem cell gene therapy) can be efficacious therapies for preventing the development of c-ALD in children [8], but AMN can develop later in life [9]. Notably, hematopoietic stem cell transplantation (HSCT) seems to be successful as a disease-modifying therapy also in subjects with AMN who develop cerebral demyelination, if they are treated as soon as cerebral demyelination occurs.

Prognosis AMN is by far the most common phenotype among the adult-onset forms of X-ALD, while c-ALD or Addison-only phenotype rarely has onset or persists in adulthood. Indeed, c-ALD most commonly presents at the age of 7 ± 2 years

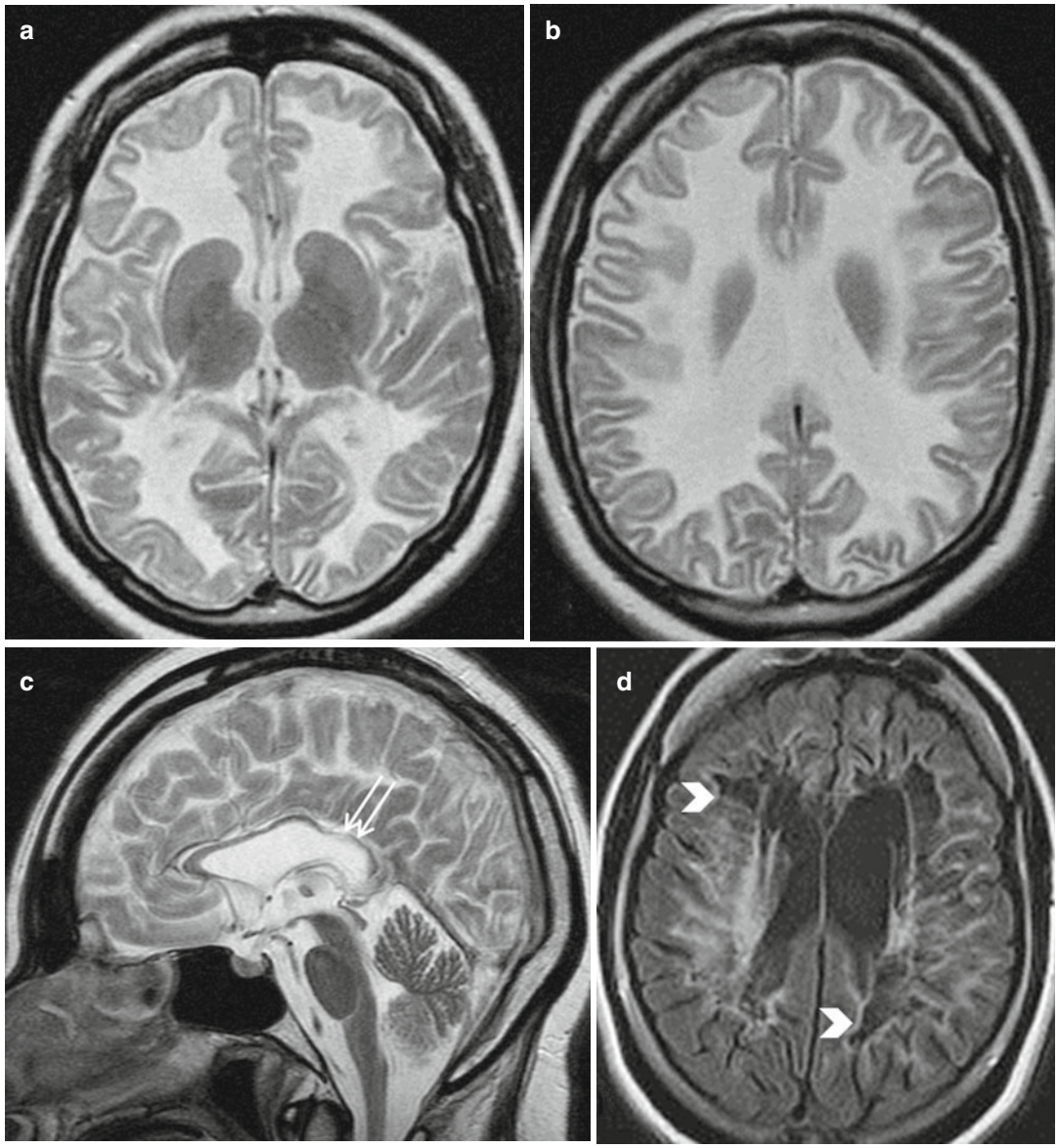

Fig. 14.2 Vanishing white matter. Axial and sagittal T2-weighted images (**a**–**c**) show extensive cerebral white matter abnormalities with involvement of "U" fibers; the corpus callosum is very thin and the inner rim of the corpus callosum is affected (**c**, *arrows*). Axial FLAIR image in an another patient (**d**) reveals almost complete disappearance of white matter with cystic degeneration (*arrowheads*)

and usually leads the patient to a vegetative state or death in 3 years or so. Signs of adrenocortical failure most commonly start between 5 and 10 years of age, but the majority of patients with adrenocortical failure – who can survive thanks to hormone replacement therapy – will develop AMN later in life [7]. The mean age at onset of AMN is 28 ± 9 years [7], but about 70 % of patients already have adrenocortical failure when the first neurological symptoms start. About 55 % of AMN patients do not develop cerebral demyelination at all ("pure" AMN), while the remaining 45 % can show cerebral lobar white matter involvement (adrenoleukomyeloneuropathy [ALMN]) on brain MRI, which may become symptomatic and variably progressive. In particu-

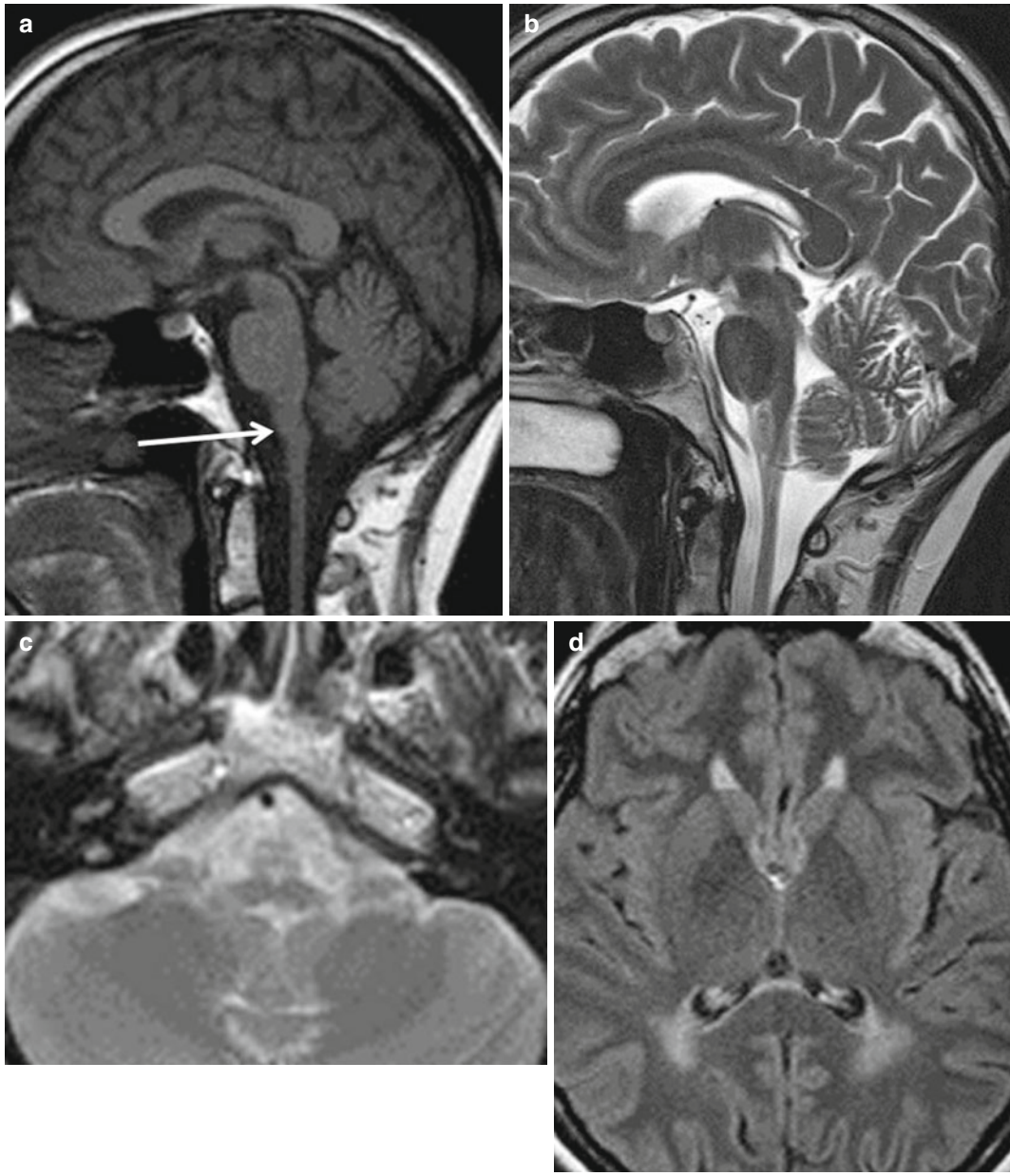

Fig. 14.3 Adult onset AxD. T1 and T2-weighted midline sagittal section (**a**, **b**) show atrophy and signal abnormalities in the medulla oblongata (*arrow*). Axial T2-weighted section (**c**) demonstrates signal hyperintensities in the atrophic anterior part of the medulla oblongata. Axial FLAIR image (**d**) shows increased signal intensity in the periventricular white matter, more extensive in the posterior regions

lar, over a period of 9.5 (±5.5) years, about 20 % of subjects with "pure" AMN can unpredictably develop severe cerebral demyelination, leading to total disability and death after a survival period of approximately 2 years (2.3 ± 1.9 years, median 1.6 years, range 0.5–7.6 years) [10]. A recent study, however, has concluded that cerebral demyelination can be higher than previously reported, given that 63 % of subjects with AMN developed brain involvement over a period of 10 (±6.9) years after the onset of myelo(neuro)pathy and died after 3.4 ± 2.9 years [11]. In "pure" AMN, walk-

Table 14.1 Adult-onset leukodystrophies

	MIM #	Mode of inheritance	Genes	Age at onset	Diagnostic tests, in addition to gene tests	Treatment available
Adrenoleukodystrophy/ adrenomyeloneuropathy	300100	X-linked	*ABCD1*	C-A	MRI, blood VLCFA	Yes
Metachromatic leukodystrophy	250100	AR	*ARSA*	C-A	MRI, arylsulfatase A enzyme activity	Yes
Krabbe disease	245200	AR	*GALC*	C-A	MRI, beta-gactocerebrosidase enzyme activity	Yes
Adult polyglucosan body disease	263570	AR	*GBE1*	A	MRI, nerve biopsy	No
Autosomal dominant adult-onset leukodystrophy	169500	AD	*LMNB1*	A	MRI	No
Hereditary diffuse leukoencephalopathy with spheroids	221820	AD	*CSF1R*	A	MRI	No
Nasu-Hakola disease	221770	AR	*TREM2, TYROBP*	A	MRI, skeletal X-rays	No
Leukodystrophy with vanishing white matter	603896	AR	*EIF2B1-5*	C-A	MRI	No
Alexander disease	203450	AD	*GFAP*	C-A	MRI	No
LBSL	611105	AR	*DARS2*	C-A	MRI	No
Pelizaeus-Merzbacher disease	312080	X-linked	*PLP1*	C(−A)	MRI	No
Pelizaeus-Merzbacher-like disease 1	608804	AR	*GJC2*	C-A	MRI	No
Leukoencephalopathy with ataxia	615651	AR	*CLCN2*	C-A	MRI	No

See the text for further details
Abbreviations: *A* adult onset, *AD* autosomal dominant, *AR* autosomal recessive, *C* childhood onset, *LBSL* leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation, *MRI* brain MRI showing a typical or pathognomonic pattern, *VLCFA* very long chain fatty acids

ing disturbances (spastic gait) seem to be followed by sensory disturbances in the legs, then by bladder dysfunction (i.e., urgency, urinary incontinence, and urinary retention), and eventually by fecal urgency and difficulty to defecate, after a mean period of 5, 6, and 12 years, respectively [10]. Overall, the progression of the handicap is gradual, with a mean of the modified Rankin score of 1.7 (±0.9) and 2.9 (±1.1) after 9.1 (±8.2) and 16.2 (±8.9) years from disease onset, respectively. In particular, AMN patients seem to need assistance to walk and they can be even wheelchair-bound about 16 years after the first neurological symptoms [10].

In their 40s, around 50 % of X-ALD female carriers, and probably more when their age increases to ≥60 years, can develop mild myeloneuropathy with impaired vibration sense and lower limb hyper-reflexia and pain, while around 15 % of cases can develop an overt spastic paraparesis with bladder dysfunctions and fecal incontinence, resembling the male AMN form [5, 6]. As a rule, however, for female carriers life expectancy remains normal, with the exception of ultra-rare cases suffering from cerebral involvement resembling the male c-ALD form.

14.3 Adult-Onset Metachromatic Leukodystrophy (MLD)

Definition Metachromatic Leukodystrophy (MLD) is a metabolic disease caused by recessive mutations in the gene arylsulfatase A (*ARSA*).

Epidemiology MLD incidence is reported to be approximately 1 in 100,000 births, with the adult form (onset after age 16) affecting 20 % of individuals with the disease (2 cases per million per year).

Clinical features Adult-onset (AO) MLD seems to be caused by mutations encoding ARSA with residual enzymatic activity (so-called R-alleles) and is characterized at onset by behavioral and cognitive decline, which may lead to the erroneous diagnosis of schizophrenia, or by walking difficulties caused by spastic paraparesis or cerebellar dysfunction. The onset is usually in the twenties, but it can also occur at age 60 or later [1, 12].

Prognosis The evolution is slowly progressive, but periods of relative stability may be seen (http://ghr.nlm.nih.gov/condition/metachromatic-leukodystrophy). Although some patients with isolated behavioral and cognitive decline at onset do not develop any neurological symptoms despite a disease duration of more than 20 years, most of them develop spastic or ataxic motor impairment over a median period of 7 years after disease onset (range 2–14 years) [12]. Similarly, patients with walking difficulties at onset usually develop neuropsychiatric symptoms over a period of months or years. Hence, the two different types of MLD patients at onset become clinically similar in advanced disease. Optic atrophy, signs of bulbar dysfunction such as dysphagia, and epileptic seizures may appear during disease evolution, and in the terminal stages, the patients have a severe dementia and eventually reach a vegetative state lying in a decorticate or decerebrate posture [1]. Subjects with AO-MLD may survive from 1 to 20–30 years after disease onset, with a mean of about 7 years [12]. Allogeneic hematopoietic stem cell transplantation (HSCT) seems to be able to halt the progression of late MLD [13], whereas lentiviral hematopoietic stem cell gene therapy seems to be effective in preventing the onset of the disease in presymptomatic subjects, thus opening a new era in the therapy of MLD [14].

14.4 Adult-Onset Krabbe Disease

Definition Krabbe disease is a rare autosomal recessive metabolic leukodystrophy caused by mutations in the galactosylceramidase *(GALC)* gene.

Epidemiology The incidence of Krabbe disease is approximately 1 in 100,000 births.

Clinical features The onset is usually in the first 6 months of life (early infantile form), and the prognosis is very poor, because the course is rapidly progressive with death within approximately 1 year after the onset. In contrast, Krabbe disease with onset in childhood can persist into adulthood [15], and HSCT can be effective in arresting the progression of the disease [16]. The adult-onset form (≥16 years) is very rare (<10 % of the individuals with the disease), and nearly constantly presents with progressive walking difficulties due to spastic paraparesis or (asymmetric) lower limb weakness. The mean age at onset in 25 patients with adult-onset Krabbe disease was 35 years, ranging from 16 to 66 years [15].

Prognosis Disease evolution is slowly progressive, but rapid decline within a few months and periods of relative stability have been reported. Walking difficulty remains the main symptom, with other neurological symptoms, such as dysarthria, cerebellar ataxia, *pes cavus*, altered vibration sense, optic atrophy/pallor, tongue atrophy/fasciculation, urinary dysfunction, and/or cognitive decline developing in a minority of subjects. The mean time to the wheelchair-bound state seems to be approximately 15 years, and severe dementia is rare [15]. Unlike the infantile form, life expectancy in adult-onset patients maybe normal (http://ghr.nlm.nih.gov/condition/krabbe-disease), although respiratory failure and aspiration pneumonia from severe dysphagia can lead to premature death [15].

14.5 Adult Polyglucosan Body Disease (APBD)

Definition Adult polyglucosan body disease (APBD) is a rare adult-onset leukodystrophy caused by autosomal recessive mutations in the *GBE* gene, encoding for the *G*lycogen *B*ranching *E*nzyme.

Clinical features ABPD is characterized by bladder dysfunction, spastic paraplegia with vibration loss, and axonal neuropathy. In general, APBD patients develop their symptoms after the age of 40 years. Bladder dysfunction is usually the first symptom, with a mean age at onset of 51 years, followed by walking difficulties and lower limb paresthesias, at a mean age of 53 years [17].

Prognosis The clinical course is progressive, with the need of a cane by mean age of 58 years, of a walker by mean age of 63 years, and of a wheelchair by mean age of 64 years. Most APBD patients develop attention and memory deficits, followed by a frank dementia in the later stages of the disease. The median life expectancy is 70 years, with no difference between men and women, and similar course among affected siblings [17].

14.6 *LMNB1*-Related Autosomal Dominant Leukodystrophy

Definition Lamin B1 (*LMNB1*)-related disease is a very rare autosomal dominant leukodystrophy (ADLD) caused by a duplication of the *LMNB1* gene encoding the nuclear lamina protein lamin B1.

Clinical features The onset of the disease is in adulthood, most frequently in the fourth to sixth decade, with pyramidal and cerebellar signs usually preceded by autonomic abnormalities (orthostatic hypotension and bladder/bowel/erectile dysfunction).

Prognosis The evolution is progressive and fatal [18]. Survival time ranged from 1 to 13 years after the disease onset, among ten deceased patients from the same three-generation family (mean age onset: 44 years; mean age at onset: 52 years) [19]. Impaired sweating and body temperature regulation was reported as the possible cause of death in one case but autonomic dysfunction seems to be an infrequent cause of death [18].

14.7 Neuroaxonal Leukodystrophies (NALDS): Hereditary Diffuse Leukoencephalopathy with Spheroids and Nasu-Hakola Disease

Definition Hereditary diffuse leukoencephalopathy with spheroids (HDLS) and Nasu-Hakola Disease (NHD) are rare adult-onset hereditary leukoencephalopathies characterized by early-onset progressive dementia and, neuropathologically, by the presence of axonal spheroids. HDLS is autosomal dominantly inherited and is caused by mutations in the colony stimulating factor 1 receptor (*CSF1R)* gene, while NHD – which is also termed polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL) – is inherited as an autosomal recessive trait and derives from mutations in the *TREM2* or *TYROBP* genes. Their pathogenic basis is a microglial dysfunction, and therefore they are considered "microgliopathies," i.e., primary *microglial* disorders of the central nervous system.

Clinical features and prognosis *CSF1R*-related HDLS usually develop in the 40s, but the age at onset may be as late as 78 years [20]. The evolution is progressive and fatal: early behavioral and cognitive decline, resembling fronto-temporal dementia, is aggravated by motor impairments with pyramidal and extrapyramidal signs (akinetic-rigid syndrome), which eventually lead the patients to be bedridden in a vegetative state. The mean survival time is 6 years, ranging from 2 to 11 or more years, with death usually resulting from pneumonia or other infections [21]. NHD develops in young adults (age at onset: 27 ± 7 years), with bone symptoms (e.g., bone pain and increased susceptibility to fractures) usually preceding the neuropsychiatric symptoms, which are similar to those of frontotemporal dementia. Notably, some patients can develop progressive dementia without any bone symptom [22; authors, personal observation]. The disease course is slowly progressive, with a mean survival of approximately 16 years (range:

3–35), characterized by early behavioral change, followed by cognitive and motor impairment which leads the patient to be bedridden in an akinetic mutism and eventually in a vegetative state. Walking difficulties may depend also on recurrent fractures, and some patients can present epileptic seizures that occasionally results in status epilepticus. Younger onset (≤ 20 years of age) seems to be associated with a better prognosis (mean survival time of 29 years, range 23–35 years) [23], although patients with late onset can also show an unusually benign clinical course [24].

14.8 Adult-Onset Leukodystrophy with Vanishing White Matter

Definition Leukodystrophy with vanishing white matter (LVWM) is a rare autosomal recessive white matter disease due to mutations in one of the five eukaryotic initiation factor 2B genes (*EIF2B1-5*), which encode for the five subunits of the guanine nucleotide exchange factor eIF2B. So far, the adult-onset form has been usually associated with *EIF2B5* mutations and occasionally with *EIF2B3* mutations.

Clinical features Psychiatric symptoms, cognitive decline, spastic paraplegia, cerebellar ataxia, and ovarian failure are key clinical manifestations.

Prognosis There is some genotype-phenotype correlation in subjects with LVWM, probably related with the degree of residual eIF2B activity. For instance, the Arg113His *EIF2B5* mutation in the homozygous state is consistently, though not always, associated with late onset and slow progression. However, there is also great inter-familial and intra-familial phenotypic variability for the same mutations, suggesting that other genetic, epigenetic, and environmental factors contribute to the phenotypic variability [25]. Unlike children, who usually survive only 2–5 years after the first clinical manifestation, adult-onset (≥16 years) LVWM is usually characterized by slower neurological progression. However, the prognosis seems to be highly variable and unpredictable for individual patients, with even relative stability over periods of years or decades [26; authors, personal observations]. In particular, 11 out of 14 patients (~80 %) suffering from adult-onset LVWM with mean age at onset of 34 years (range 16–62) had lost independent walking when evaluated after a mean follow-up of 13 years (range 3–22). The remaining 3 out of 14 patients (~20 %) – with a mean age at onset of 21 years (range 16–27) – were still able to walk independently when evaluated after a mean follow-up of 6 years (range 5–7) [26]. Moreover, 8 out of 14 patients (~60 %) with mean age at disease onset of 33 years (range 17–62) were cognitively impaired with a mean MMSE (Mini Mental State Examination) score of 17 (range 0–27) when evaluated after a mean follow-up of 11 years (range 3–22). Notably, a 16-year-old asymptomatic patient remained asymptomatic with normal cognitive functions at age 23 years, after a 7-year follow-up [26]. Stressful emotional and physical situations (e.g., extreme temperatures or even fright) as well as febrile infections, mild head trauma, seizures, major surgical procedures, and delivery can cause acute deterioration leading to death in a few months if not days [26, 27]. Accordingly, in the case series reported by Labauge et al. [26], two patients died in their 30s after a stress-induced deterioration. One died rapidly after a short generalized seizure which led to an intractable *status epilepticus*; the second died 8 months after a mild head trauma without initial loss of consciousness, which led to a comatose state associated with irreversible brain edema.

14.9 Adult-Onset Alexander Disease

Definition Alexander disease (AxD) is a rare leukodystrophy inherited as an autosomal dominant character, but penetrance can be incomplete, and sporadic cases with *de novo* mutations have been reported. It is the first discovered example of primary astrogliopathy, because it results from

a defect in astrocytes caused by mutations in the *GFAP* gene, encoding the intermediate filament glial fibrillary acidic protein (GFAP). The severity of the disease is highly variable, with no clear genotype-phenotype correlation.

Clinical features The *AxD type I* is the most severe form, accounts for about 60 % of cases, and has its onset between birth and the age of 4, usually before age 2. Death usually occurs in the first year of life when onset occurs within the first 30 days of life, and in the first two decades of life when onset is later; AxD type I only rarely persists in adulthood [28]. The *AxD type II* accounts for about 40 % of cases and has its onset commonly in late adolescence or adulthood (after the age of 12 years), although more rarely it can develop in childhood (after the age of 4) and persists into adulthood because of the natural history and/or a better supportive therapy [28]. Patients with onset in their 60s or even later have also been reported [29], but it is impossible to predict whether asymptomatic individuals carrying familial *GFAP* mutations will develop the disease, and, if so, at what age. AxD type II is characterized by walking difficulties due to spasticity and/or ataxia, brainstem symptoms (dysarthria, dysphonia, dysphagia, sleep apneas and snoring, palatal myoclonus), bladder dysfunction, dysautonomia, and (kypho-)scoliosis. The evolution is usually slowly progressive, but some patients can have a fluctuating course, particularly in the early phases of the disease, or a rapid progression leading to death in a few years [29]. Eventually, the patients become wheelchair-bound or confined to bed because of motor spastic and ataxic impairment, while cognition seems to be usually well-preserved. Assessment and early management of dysphagia, sleep apnea, vocal cord palsy in adduction position [29], and scoliosis can greatly improve the quality and duration of life. The most common causes of death are aspiration pneumonia and respiratory failure of different origin, which were reported in a few patients with adult-onset AxD type II after a period of 1.5–20 years of disease [29]. In agreement with this observation, a subsequent, unpublished review of the literature performed by the authors revealed that the median survival time of 15 subjects with adult-onset AxD type II was 12 years, with a range from 2 to 34 years. Moreover, the median survival of all the subjects with AxD type II (i.e., including those with age at onset <16 years) has been reported to be 25.0 ± 2.1 years [28].

14.10 Leukoencephalopathy with Brainstem and Spinal Cord Involvement and Lactate Elevation (LBSL)

Definition and clinical features LBSL is a very rare disease caused by recessive mutations in the *DARS2* gene, which encodes the mitochondrial aspartyl-tRNA synthetase. The most common neurological sign is cerebellar ataxia, particularly gait ataxia.

Onset of disease usually occurs during childhood but adolescent-onset (>12–18 years) and adult-onset (≥18 years) cases are described [30].

Prognosis Disease prognosis is better than for other hereditary leukoencephalopathies and mainly depends on the age at onset of the neurological signs, with late-onset cases showing slower progression. Ambulation is generally more severely affected than manual skills, while cognitive abilities are usually normal. Accordingly, adult-onset individuals may have a normal life expectancy, but they usually become ambulant with support and eventually wheelchair-bound. By contrast, individuals with infantile onset (<2 years) may never achieve unsupported walking and can present a rapid deterioration that leads to death in a short period of time [30].

14.11 Hypomyelinating Leukodystrophies

Definition The term "hypomyelinating leukodystrophy" refers to a heterogeneous group of hereditary leukoencephalopathies characterized by a diffuse, mild T2-weighted and FLAIR-

weighted hyper-intensity of the cerebral white matter involving also the U-fibers and with typical onset in childhood [31].

Pelizaeus-Merzbacher Disease (PMD), now termed hypomyelinating leukodystrophy type 1 (HLD1), is the prototype of this group of diseases, and is due to mutations in the proteolipid protein 1 (*PLP1*) gene, which is located on chromosome X. Other ultra-rare forms of hypomyelinating leukodystrophies include the autosomal recessive Pelizaeus-Merzbacher-like disease type 1 (PMLD1), also termed HLD2 and associated with *GJC2* mutations, and the autosomal dominant hypomyelinating leukodystrophy with atrophy of the basal ganglia and cerebellum (H-ABC), also termed HLD6 and caused by *TUBB4A* mutations.

Clinical features PMD can present exceptionally in adulthood, most commonly in females who develop a progressive spastic paraplegia associated with bladder/bowel dysfunctions and unremarkable brain MRI (so-called spastic paraplegia (SPG2) phenotype). In contrast, the onset of PMD in males is always in the first months-years of life with nystagmus, developmental delay, muscular hypotonia, followed by mental retardation, spasticity, and optic atrophy, although the disease can *persist* into adulthood because of its slow evolution and better supportive care.

Prognosis Depending on the maximal level of motor acquisition, the severity of the disease in adult patients is largely variable, ranging from subjects who achieved only head control during their childhood to patients who are still able to walk at the age of 30 years or more. *PLP1* mutations affecting the 277 amino acid proteolipid protein (PLP) but not its 242 amino acid isoform DM20 seem to be associated with relatively mild phenotypes [32].

Only a few cases of PMLD1 with onset in late adolescence or early adulthood have been described so far [33]. These subjects have a mild phenotype characterized by slowly progressive spastic paraplegia with ability to walk – with or without support – after 20 years or more from disease onset [33]. Moreover, the authors have experience with a case of subclinical hypomyelinating leukodystrophy caused by a *GJC2* mutation incidentally found in a 30-year-old woman who is still free of symptoms after approximately 5 years of follow-up [34]. Notably, the classical form of PMLD1 with onset in the first months-years of life is associated with complete loss-of-function *GJC2* mutations, whereas these subclinical or adult-onset phenotypes have been associated with partial, mild, or moderate, loss-of-function *GJC2* mutations, suggesting a strong genotype-phenotype correlation [34].

14.12 *CLCN2*-Related Leukodystrophy and Radiologically Isolated Leukoencephalopathies

Definition and clinical features *CLCN2*-related disease, also termed leukoencephalopathy with ataxia (LKPAT), is a recently discovered autosomal recessive leukodystrophy caused by mutations in the *CLCN2* gene encoding ClC-2, a chloride channel implicated in brain ion and water homeostasis. It is characterized by specific MRI findings caused by chronic white matter edema, which usually leads to a mild cerebellar ataxia associated with a varying combination of other neurological signs. The age at onset ranges from childhood to middle age.

Prognosis Despite impressive brain MRI abnormalities, the evolution usually seems to be very slowly progressive or even stable over decades, and it can be incidentally discovered on imaging in asymptomatic subjects [35, 36; authors, personal observations]. We believe that this recently defined leukodystrophy is a good example of what we call clinical-neuroimaging dissociation, i.e., the lack of correspondence between the severity of white matter abnormalities on brain MRI and the extent of clinical impairment. Of note, this dissociation can be occasionally observed in subjects – typically middle-aged women – with extensive white matter changes resembling a leukodystrophy, but without overt neurological symptoms and even neurophysiological changes despite a follow-up of years (authors, personal observations). We call this condition "radiologically isolated leukoencephalopathy" (RIL). The nature of RIL is unknown but, given the lack of

clinical and laboratory findings supporting acquired diseases, it might be inherited. Therefore, it should be kept in mind that, especially in women, an incidentally found "leukodystrophic" pattern can remain "asymptomatic" for years, decades, and maybe for an entire life.

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Antibody-Mediated Encephalitis

15

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Key Facts

- **Terminology and definition** – Encephalitis caused by antibodies directed against antigens located on the surface of neurons
- **Clinical features** – Acute/subacute onset of psychiatric symptoms, memory deficits, and seizures (limbic encephalitis [LE]), or more diffuse CNS involvement with movement disorders, coma, hypoventilation, and dysautonomia.
- **Diagnostic markers**
  - **CSF** – Increased lymphocytes and protein content and intrathecal IgG in about 50 % of patients; neuronal surface antibodies (NSAb) (in serum and CSF)
  - **MRI** – Often normal or nonspecific; medial temporal lobe T2-hyperintensity in LE
  - **Electroencephalography**: Slow waves, temporal lobe epileptic activity
  - Pathology (variable depending on Ab association); IgG and complement deposits gliosis, neuronal loss, B cells and plasma cell infiltrates).
- **Top differential diagnosis** – Infectious encephalitis, paraneoplastic limbic encephalitis, prion disease and degenerative disorders, temporal lobe epilepsy.
- **Priciples of treatment** – Immuno and antineoplastic (in the presence of a tumor) therapies.
- **Prognosis** – Anti-VGKC encephalitis often causes residual amnestic deficits. Anti-NMDR encephalitis has 80 % favorable autcome.

Abbreviations

CNS, central nervous system; DPPX, Dipeptidyl-peptidase-like protein-6; EEG, electroencephalogram; FBDS, Faciobrachial dystonic seizures; LE, Limbic encephalitis; LGI1, leucine-rich glioma-inactivated 1; mGluR5, Metabotropic glutamate receptor 5; NMDA, *N*-Methyl-D-aspartic acid; NSAb, neuronal surface antibodies; NSAbs, anti-neuronal surface antibodies; PERM, progressive encephalomyelitis with rigidity and myoclonus; PNS, paraneoplastic neurological syndrome; REM, rapid eye movements; VGKC, voltage-gated potassium channels

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15.1 Definition

Antibody-associated encephalitis (alias: autoimmune encephalitis, central nervous system neuronal surface antibody-associated syndromes) are a group of immunotherapy-responsive diseases affecting the central nervous system (CNS) caused by antibodies against antigens located on the surface of neurons (NSAbs).

Initially recognized in the paraneoplastic context, it is now established that these diseases can occur with or without tumor association. Thus, they are distinct from diseases associated with antibodies against intracellular neuronal antigens (onconeural antigens) which invariably are markers of underlying tumor (classical paraneoplastic syndromes).

15.2 Clinical Features

Patients present with acute or subacute onset (days to weeks) of classical limbic encephalitis (psychiatric disturbances, memory deficits, and seizures) or with more diffuse involvement of the CNS. The clinical picture and the association with tumors vary according to the related antibody. Most patients with a form of antibody-associated autoimmune encephalitis harbor antibodies against the VGKC-complex protein LGI1 and NMDA-type glutamate receptor.

- *Anti-LGI1 (VGKC-complex) encephalitis*. Less than 11 % cases are paraneoplastic (lung cancer, thymoma) [1, 2]. Male predominance. Usually typical limbic encephalitis (LE); faciobrachial dystonic seizures (FBDS) can precede the florid phase [3]; hyponatremia and REM-sleep behavior disorders are also reported.
- *Anti-NMDA receptor encephalitis*. More frequent in the pediatric age group and in young women; 30–40 % are paraneoplastic and generally associated with ovarian teratoma, especially in young women. Multistage symptoms preceded by prodromes (e.g., cough, fever, headache): psychiatric symptoms, cognitive deficits, seizures, movement disorders, dysautonomia, stupor or coma, hypoventilation.

Less common NSAb-associated encephalitis:

- *Anti-GABAb receptor encephalitis*. 50 % of patients harbor a small-cell lung cancer; typical LE with prominent seizures [4].
- *Anti-Caspr2 (VGKC complex) encephalitis*. Some cases are associated with thymoma. Peripheral nerve hyperexcitability with dysautonomia, sleep disorders, psychiatric features, and seizures (e.g., Morvan syndrome) [2–5].
- *Anti-AMPA receptor encephalitis*. Most cases are paraneoplastic (lung, breast, and thymus). Typical limbic encephalitis, with prominent memory deficits and psychiatric symptoms [6].

Further NSAb have recently been reported:

- Against glycine receptor (α1 subunit): progressive encephalomyelitis with rigidity and myoclonus (PERM; variant of Stiff Person Syndrome)
- Against anti-dipeptidyl-peptidase-like protein-6 (DPPX), a subunit of Kv4.2 potassium channels: encephalitis characterized by agitation, myoclonus, seizures and diarrhea at the onset
- Against metabotropic glutamate receptor 5 (mGluR5): in two patients with LE and Hodgkin lymphoma (Ophelia syndrome)
- Against the D2 subunit of the dopamine receptor in basal ganglia encephalitis with psychiatric disturbances and movement disorders

Anti-GAD antibodies are not directed against surface antigens but should be considered in the diagnosis of autoimmune encephalitis since they have been found in women with limbic encephalitis with prominent temporal lobe epilepsy [7].

15.3 Diagnosis

If the clinical and paraclinical features are typical of a well-defined syndrome such as LE, the presence of an NSAb in the serum and/or CSF will confirm the diagnosis. In other cases, the exclusion of other potential causes should prompt the search for NSAb and onconeural antibodies and

at the same time would justify a trial of immunotherapy. A diagnosis of autoimmune encephalopathy, with variable levels of evidence, will be subsequently based on NSAb presence and/or response to treatment [8].

MRI Is often nonspecific; T2-weighted medial temporal lobe hyperintensity is a common finding especially in anti-LGI1, GABAbR, and AMPAR; temporal lobe hyperintensity is a common finding in a post-seizure phase. In anti-NMDAR, lesions can affect futher cortical areas.

Functional nuclear images: Cortical hypermetabolism especially in the acute phase.

Electroencephalogram (EEG) Slow waves, disorganized activity, or epileptic activity. Dyskinetic movement disorders of NMDAR encephalitis are usually nonepileptic [9]; faciobrachial dystonic features of LGI1 encephalitis are epileptic [10].

CSF Inflammation (increased lymphocytes and protein content); specific oligoclonal bands or elevated IgG index; A normal CSF does not exclude the diagnosis.

The search for NSAbs should be performed on serum and CSF of patients on a cell-based assay.

15.4 Pathology

B cells and plasma cell infiltrates. Anti-VGKC-complex: complement deposition with acute neuronal death; anti-NMDAR: poor tissue injury and neuronal loss [11].

15.5 Top Differential Diagnosis

Infectious (e.g., herpetic encephalitis, neurosyphilis, Creutzfeldt-Jakob disease)
Autoimmune (e.g., paraneoplastic disorders, vasculitis)
Toxic-metabolic (e.g., Wernicke-Korsakoff encephalopathy, neuroleptic malignant syndrome)
Epileptic (e.g., temporal lobe epilepsy, nonconvulsive status epilepticus)
Degenerative (e.g., rapidly progressive dementia)
Tumoral (e.g., temporal glioma, CNS lymphoma)

15.6 Prognosis

In recent years, a growing number of autoantibodies targeting neuronal surface or synaptic antigens have been reported in patients with neurological symptoms suggestive of a paraneoplastic neurological syndrome (e.g., limbic encephalitis). However, these autoantibodies, different from "onconeural" antibodies, are generally not associated with a tumor and are predictive of immunotherapy response. This led to a reclassification of autoimmune autoantibody-associated encephalopathies (and other syndromes) based on the localization of the antigens (intracellular vs. extracellular/surface). This distinction has mainly prognostic implications as syndromes associated with neuronal surface antibodies (NSAS) generally have a much better outcome [8].

Although these syndromes have begun to be widely recognized, most NSAbs have only recently been described; there is no information on their incidence and the full clinical spectrum has still not been completely defined.

It is generally recognized that the prognosis is good when compared with classical paraneoplastic syndromes but presentation, severity, and outcome can be variable. Case series comparing different causes of encephalitis showed that antibody-associated autoimmune encephalitis seems to have a poorer outcome than other etiologies (i.e., infectious). This probably represents a selection bias as these studies tend to include only severe forms of encephalitis [12, 13].

The factors that may influence the outcome in NSAb-associated autoimmune encephalitis have not been clearly elucidated yet, with the partial exception of anti-NMDAR encephalitis. Antibody type and timing of immunotherapy are probably the most important prognostic factors. Encephalitis associated with VGKC-complex-Ab and those that receive an earlier treatment generally have a better outcome than those with

NMDAR-Ab and those in which immunosuppression is delayed. Other possible prognostic factors are the presence of malignancy, the antibody titer, and persistent intrathecal synthesis of autoantibodies.

The two therapeutic strategies are immunotherapy (first-line immunotherapy, including corticosteroids, IVIG, and plasma exchange) and antineoplastic treatment if a tumor is found. However, evidence regarding treatment of NSAb-associated encephalitis comes largely from Class IV studies.

15.6.1 Anti-VGKC-Complex Abs Encephalitis

Few retrospective data are available on treatment and outcome of patients with VGK-complex Ab and particularly with LGI1-Abs. First-line immunotherapies (corticoids, IVIG, PE) are generally effective in most patients. However, although substantial recovery is seen after immunotherapy, patients often show residual amnestic deficits that may associate with temporal lobe atrophy [14]. Possible predictors of cognitive outcome are age at onset, delay from symptom onset to initiation of treatment, and VGKC-Ab titer [15].

Faciobrachial dystonic seizures (FBDS) are consistently associated with LGI1-Abs and often precede the overt manifestation of LE [10]. In LGI1-Abs-associated FBDS-LE, administration of immunotherapy, particularly corticosteroids, is associated with a marked reduction in seizures that had been refractory to anti-epileptic drug, while relapses of FBDS occurred after corticosteroid dose reductions [3]. Recognition of FBDS should prompt testing for LGI1 Abs and immunotherapy to possibly prevent the development of LE [10].

LGI1-Abs are rarely associated with cancer while CASPR2-Abs can associate with thymoma in up to 30 % of cases. The presence of a tumor is a bad prognostic factor, independent of immunotherapies and antibody subtype [2, 16]. Relapses have been reported in less than 10 % [1].

15.6.2 Anti-NMDAR Abs Encephalitis

Anti-NMDAR encephalitis is usually more severe than LE associated with VGKC-Abs as it can present with diffuse encephalic involvement, dysautonomia, and hypoventilation that may need intensive care. Nevertheless, it generally has a good prognosis with tumor treatment and immunotherapy [17]. Data on prognosis and response to treatment have been confirmed in a large series of 577 patients showing that about 80 % have a favorable outcome [18]. About half of the remaining patients have residual severe cognitive deficits or psychiatric sequelae and the other half are at risk of death, although this is probably an overestimation [18]. Otherwise, in older people (>45 years), the disorder is less common and severe but the prognosis is worse, probably due to a delay in diagnosis and treatment [18].

Two independent predictors of good outcome are low severity of symptoms (i.e., no need for admission to an intensive care unit) and the prompt initiation of immunotherapy and tumor removal [18]. High antibody titers are associated with poor outcome and the presence of a teratoma; an early decrease of CSF antibody titers during the first months is associated with good outcome [19].

Different from initial findings, the proportion of cases associated with teratoma has been found to be smaller (about 30–40 %) and unlike classical (T-cell mediated) paraneoplastic syndromes, the presence of a tumor is not a negative prognostic factor [17, 20]. Treatment should be initiated promptly with first-line immunomodulation (corticosteroids followed by IVIG or plasma exchange) and teratoma resection. Second-line treatment with rituximab or cyclophosphamide in nonresponsive cases has been proposed [17]. In the largest published series, 92 % of patients underwent first-line immunomodulation resulting in improvement within the first 4 weeks of treatment in 53 % of patients; 97 % of them showed good outcome at 24-month follow-up (modified Rankin Score of 0–2). The remaining 47 % of patients who did not improve in the first month and who received

rituximab, cyclophosphamide, or both had better outcomes than did those who continued with first-line immunotherapy or who received no further treatment [18].

Neurological relapses are present in 10–20 % of cases and are less common in patients who receive second-line immunotherapy during the initial episode of encephalitis [18].

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Dementias

16

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Abbreviations

AD, Alzheimer disease; ADLs, activities of daily living; bvFTD, behavioral variant of FTD; CJD, Creutzfeldt-Jakob disease ; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; FTD-MND or FTD-ALS, motor neuron disease; LBs, Lewy bodies; MCI, mild cognitive impairment; ns, nothing specific; PEG, percutaneous endoscopic gastrostomy; PFA, progressive fluent aphasia; PNFA, progressive non-fluent aphasia; SD, semantic dementia; VaD, vascular dementia; VH, visual hallucinations

16.1 Terminology and Definitions

Dementia is a syndrome characterized by cognitive and functional decline and, although not invariably, by behavioral changes.

16.2 Demographics

Alzheimer disease (AD) represents approximately 60 % of all dementias with a prevalence of 5 % in people of 65 years and older. After the sixth decade, the prevalence of Alzheimer disease in the general population doubles every 5 years, reaching 50 % for people aged above 90. Age is therefore the main risk factor, with a slight female preponderance.

Frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB) are second only to Alzheimer disease among degenerative dementias. Below age 60, however, FTD is at least as frequent as Alzheimer disease.

Vascular dementia (VaD), usually resulting from either multiple strokes or a single, strategically situated cerebral infarct, is likely to be the second most common type of dementia, but it is not degenerative. Requisite for diagnosis is the presence of relatively short temporal intervals (usually a few months) between the stroke(s) and the onset of dementia.

There are many other conditions causing symptoms of dementia, including some that are potentially reversible, such as normal pressure hydrocephalus, thyroid problems, or deficiency of vitamins. However, dementias secondary to potentially treatable causes account for no more than 5 % of cases.

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16.3 Alzheimer Disease (AD)

Key Facts

- **Terminology and definitions** – Alzheimer disease is the prototype of degenerative dementias characterized by relentless cognitive and functional decline.
- **Clinical features** – Loss of memory and of a further superior cortical function.
- **Diagnostic markers** – Definite AD requires clinical criteria and pathological evidence.
  - **CSF** – Decrease of beta-amyloid and increase of t-tau and p-tau proteins.
  - **Genetics** – Autosomal dominant mutations of APP, presenilin 1 and 2 genes in approximately 5 % of the patients.
  - **TC and MR** – Temporal/parietal atrophy with disproportionate hippocampal involvement.
- **Top differential diagnoses** – Mild cognitive impairment; frontotemporal dementia; dementia with Lewy bodies; vascular dementia; corticobasal degeneration; Creutzfeldt-Jakob Disease.
- **Prognosis** – Mean survival 10.3 years; range 2–20 years.
  - Principles of treatment (cholinesterase inhibitors, NMDA receptor antagonists).

16.3.1 Terminology and Definitions

Also known as senile dementia of Alzheimer type or primary degenerative dementia, AD is the prototype of insidious and slowly progressive dementias. Although the first cognitive symptoms generally appear so subtly as not to be immediately perceived, they gradually become worse until the person's ability to perform everyday activities is hindered.

16.3.2 Clinical Features and Diagnostic Criteria

AD onset is usually late in life (above age 65). The earlier the onset, the higher the likelihood that the patient is affected by a familiar (rather than a sporadic) form of disease with an autosomal dominant pattern of inheritance, although familiar AD accounts for only 5 % of all cases of AD. According to NINCDS-ADRDA criteria [1], the diagnosis of AD is deemed to be "probable" in the presence of an acquired memory impairment and at least another deficit among aphasia, apraxia, agnosia, and executive dysfunction. An AD diagnosis remains however "possible" even in the absence of memory deficits or, alternatively, when memory deficits, although clearly detectable, have been preceded or are overwhelmed by visuospatial dysfunction (posterior cortical atrophy) or behavioral changes (frontal variant of AD). In any case, an absolute diagnostic certainty requires pathological confirmation ("definite" AD).

The identification of a dementia syndrome followed by the diagnosis of AD essentially through an exclusionary process is the mainstay of NINCDS-ADRDA criteria [1]. Predementia stages of AD have various designations, among which amnestic MCI and prodromal AD [2] are the most commonly used. While the designation of prodromal AD refers to a specific disease (AD at the stage of its earliest clinical manifestations), that of amnestic MCI refers to a syndrome, since up to one third of subjects with amnestic MCI may evidence non-AD primary pathologies. Thus, additional clinical and laboratory (MRI, PET, CSF) features are required to support the hypothesis that the subject's amnestic MCI is indeed attributable to prodromal AD [2].

16.3.2.1 Clinical Stages

AD progression is greatly variable but, typically, proceeds through four general clinical stages.

In the first stage (amnestic MCI – prodromal AD), cognitive impairment is generally restricted to memory. Complex activities of daily living are usually spared. Further progression of disease is common, but not invariable.

In the second stage (mild dementia: lasting 2–4 years), although memory dysfunction remains prominent, deficits involving other cog-

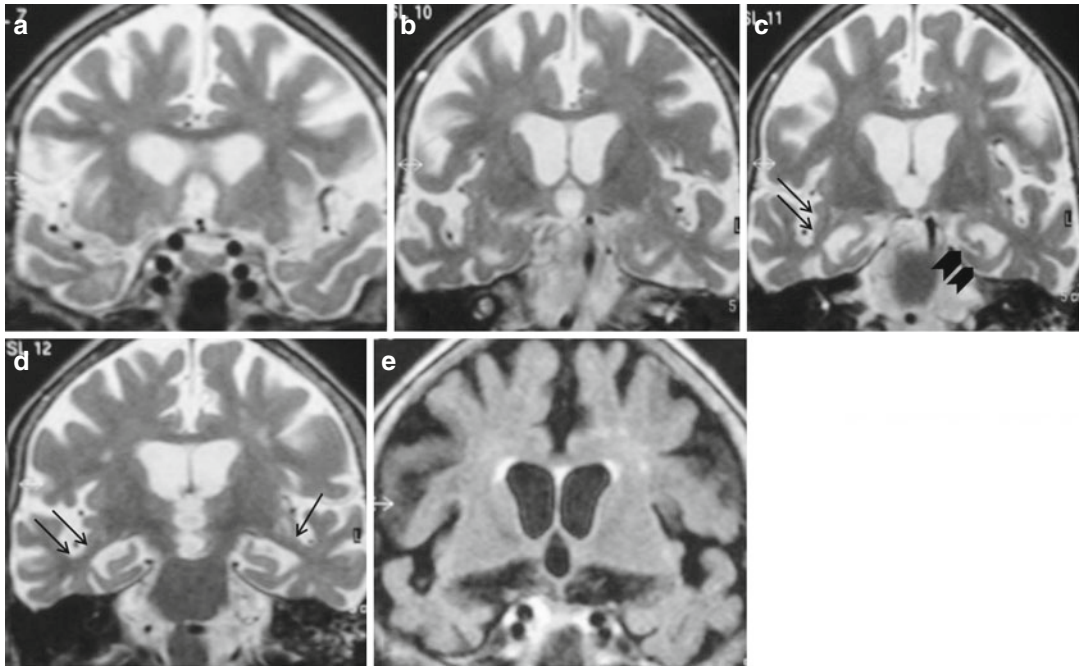

Fig. 16.1 AD. Coronal T2-weighted images from anterior to posterior (**a**–**d**), and coronal FLAIR image (**e**). The T2 images show enlargement of the lateral ventricles and cortical sulci. Note the marked hippocampal and parahippocampal gyrus atrophy (*arrowheads* in **c**) and thinning of the temporal isthmus (*arrows* in **c** and **d**). In (**e**), basal cisterns enlargement and horizontalization due to atrophy of the basal forebrain is demonstrated

nitive domains (attention, executive functions, language, problem solving) appear and complex ADLs are invariably impaired. Further disease progression is inevitable.

In the third stage (moderate to severe dementia: lasting 2–10 years), the cognitive deficits progressively worsen so as to impair basic functions, including maintaining personal hygiene and walking safely.

In the fourth stage (vegetative: lasting 1–3 years), the patient has completely lost his/her autonomy. He/she is incontinent, wheelchair bound, and unable to communicate and feed himself/herself.

16.3.3 Diagnostic Markers

CT scan, EEG, and CSF analyses were recommended in the past as procedures for excluding non-AD dementias.

Biomarkers More recent attempts to detect AD in its earliest pre-dementia phases have emphasized the need for AD-specific biomarkers, including specific patterns on morphological and structural (MRI) (Fig. 16.1) and functional (PET) neuroimaging as well as CSF levels of Abeta 42, total-tau, and phospho-tau proteins.

According to recent diagnostic criteria [2], AD can be identified even before the onset of dementia, provided that there is an episodic memory impairment, that such impairment has specific characteristics (no substantial improvement with cueing or recognition testing), and that there is at least another feature among medial temporal atrophy, temporal-parietal hypometabolism, and CSF biomarker abnormality (low Abeta 42, high total tau, high phosho-tau levels, or a combination of the three). Diagnostic accuracy is predicted to be increased when structural, metabolic, and biochemical changes are all present.

16.3.4 Pathology

Senile plaques and neurofibrillary tangles are the typical lesions observed in the brains of AD patients but neocortical plaques and allocortical tangles can also be found in many non-demented elderly people. Although the presence of tangles in the neocortex is believed to be a specific marker of disease, a cerebral biopsy is usually not performed for diagnostic purposes.

16.3.5 Top Differential Diagnosis

MCI, FTD, DLB, VaD, CJD, metabolic, infectious, toxic, alcoholic encephalopathies.

16.3.6 Therapy

Therapy of AD is based on five main drugs approved by the US FDA and the European Medicines Agency. Donepezil, galantamine, rivastigmine, and tacrine are cholinesterase inhibitors while memantine is the first in a novel class of medications acting on the glutamatergic system by modulating NMDA-type glutamate receptors. An examination of the data available from randomized clinical trials on cholinesterase inhibitors reveals that statistically significant treatment effects were consistently documented for all of the above-mentioned cholinesterase inhibitors on both the main neuropsychological (ADAS-cog) and global (CIBIC-plus) outcome measures. Nonetheless, treatment effects were modest (ranging from 2 to 5 points on the ADAS-cog) and largely secondary to continuing decline of placebo patients along the course of the trials. In general, trial duration was generally relatively short (6 months to 1 year), raising questions on the persistence of drug effect over the course of an illness that lasts much longer (3–20 years). Furthermore, areas of activities of daily living (ADLs) and quality of life were not sufficiently regarded. Tacrine was the first marketed cholinesterase inhibitor for AD treatment but due to the presence of serious adverse effects (nausea, vomiting and, especially hepatic toxicity that, although reversible, would require frequent lab monitoring) this drug never reached widespread use in AD. There is no convincing evidence that one cholinesterase inhibitor is superior to the others. Compared to the effect of cholinesterase inhibitors, that of memantine is even more modest and it is clearly documented only beyond mild-stage disease. The benefit of the combination of donepezil and memantine over donepezil alone has recently been questioned.

16.3.7 Prognosis

AD is a chronic disease with a long preclinical course. Since the beginning of the illness is insidious and poorly characterized, the diagnosis of AD is often delayed for 3–5 or more years. The median duration of AD from onset to death is 9–10 years [3], but a wide variability is seen with some subjects living less than 5 years and others up to 20 years and more. This variability in survival estimates has several explanations, including the difficulty in precisely dating the onset of the illness and the presence of real inter-individual differences in its rate of progression. Increased age and greater dementia severity adversely affect survival [4]. The course of AD can be measured by monitoring the progression of either cognitive or functional impairment. The annual decline on the Mini Mental State Exam (MMSE) is, on average, of 3–4 points. However, the progression of the illness is not linear. In fact, following a sigmoid pattern of decline, MMSE scores are usually reduced by 1–2 points per year in the first few years and by 4–5 points per year in moderate-severe stages of disease. Thus, the more severe the dementia, the faster the rate of cognitive decline is. Other factors that have been reported to be associated to a faster rate of decline and/or shorter survival are the development of parkinsonism, psychotic symptoms, and early language disturbances.

In a study performed in a primary care setting, patients with a recent diagnosis of dementia (within 12 months) had an adjusted mortality rate

at least 3 times higher than those without dementia [5]. The median survival for people in the sixth decade at diagnosis was 6.7 years, falling to 1.9 (0.7–3.6) years in those aged 90 years and over. Lower survival in this [5] than in prior studies are probably explained by greater sample heterogeneity (representing all dementia subtypes, not specifically AD) and relatively later identification of dementia.

Dementia due to AD is a major cause of death in the developed world. Advanced dementia is associated with a risk of death that reaches 25 % at 6 months (median survival 1.3 years). Life expectancy in people with advanced dementia is similar to that of people with other end-of-life conditions, such as metastatic breast cancer and stage IV congestive heart failure. In a recent study of 323 elderly (mean age 85.3 years), nursing home residents with advanced dementia (mainly due to AD), over a half (55 %) died within 18 months of baseline. During the follow-up period, pneumonia, febrile non-pulmonary episodes, and eating problems were, respectively, reported for 41 %, 53 %, and 86 % of the subjects. The 6-month mortality rate for those who had pneumonia was 47 %, while for subjects who had a febrile non-pulmonary episode or an eating problem was respectively 45 % and 39 %. Of note, in the last 3 months of life, 41 % of residents underwent at least one burdensome intervention (hospitalization, emergency room visit, parenteral therapy, or tube feeding) without any apparent advantage [6].

A specific prognostic issue in dementia is nursing home placement. In the USA, about 80 % of AD patients are institutionalized within 60 months of illness regardless of age of onset and spend one fourth of their residual survival in nursing homes. Increased duration and severity of illness, inability to walk, psychotic and other behavioural symptoms are all factors leading to earlier institutionalization.

16.3.7.1 Enteral Tube Feeding

The use of enteral tube feeding [by a nasogastric tube or percutaneous endoscopic gastrostomy (PEG)] for patients with advanced dementia who develop problems with eating or swallowing or have poor nutritional intake is common. In one US survey, one third of 186,835 nursing home residents with advanced dementia were tube fed but, despite its wide use, potential benefits (prolonging survival, improving quality of life, better nourishment, decreased risk of pressures sores) and harms (increased risk of developing pneumonia due to inhaling small food quantities and even death) of this procedure remain unclear [7]. No randomized clinical trial has so far been carried out in this field and available data are limited to a few observational controlled studies. Heterogeneity in primary outcome measures, with some studies assessing survival and others only nutritional status or quality of life, has contributed to insufficient evidence.

16.3.7.2 Hospitalization and Delirium

Delirium in the elderly predicts sustained poor cognitive and functional status and increased likelihood of nursing home placement after a medical admission. Delirium is an independent predictor of adverse outcomes in elderly hospitalized patients, particularly in the presence of cognitive impairment or dementia at baseline, and it is associated with an increased mortality rate and acceleration of cognitive decline [8]. Delirium in dementia is often unrecognized. It should be highlighted that disruptive behavior in dementia may be due to underlying delirium, and medications for treating behavioral disturbances may worsen or further mask the problem. Unfortunately, behavioral changes in dementia are often misattributed to fluctuations, diurnal variations of symptoms (sundowning), or to the underlying dementing illness itself rather than to a superimposed delirium. A delay in diagnosis of delirium and its underlying cause contributes to the poor outcomes associated with delirium superimposed on dementia. Hypoactive delirious patients appear to be at particular risk because of complications from aspiration and inadequate oral nutrition as well as falls and pressure sores. The prevalence of delirium superimposed on dementia is high. In a review where 14 studies were considered, including 7 prospective studies, 3 retrospective studies, 2 cross-sectional studies, and 2 clinical trials, the prevalence of delirium superimposed on dementia

ranged from 22 to 89 % of hospitalized or community population people aged 65 and older [9]. In the year following hospitalization, AD patients manifest a more rapid progression of cognitive impairment, increased mortality, and greater chance of definitive institutionalization. Approximately one out of eight hospitalized patients with AD who develop delirium will have at least one adverse outcome, including death, institutionalization, or cognitive decline, associated with delirium [10]. Specifically, for hospitalized patients with AD, approximately 1 in 16 deaths, 1 in 7 institutionalizations, and 1 in 5 cases of accelerated cognitive decline within 1 year can specifically be attributed to delirium [10]. However, if the causative factor is rapidly corrected, recovery can be complete. Delirium present at discharge from the hospital is associated with a 2.6-fold increased risk of death or nursing home placement, and delirium persisting after hospital discharge is associated with a 2.2-fold risk of death within the following year [8].

These figures emphasize the importance of early recognizing and preventing delirium in persons with dementia, through the implementation of a risk factor reduction strategy targeting sleep deprivation, immobility, sensory impairment, dehydration, metabolic disorders, abuse of psychoactive drugs and the elimination of unnecessary medications.

16.4 Mild Cognitive Impairment (MCI)

Key Facts

- **Terminology and definitions** – Mild Cognitive Impairment (MCI).
- **Clinical features** – Deficit in one cognitive domain, not impairing daily functions. MCI may be: (1) "amnestic", with preeminent memory and/or (2) nonamnestic, with subtle decline in function(s) not related to memory.
- **CSF, Genetics, Imaging** – ns.
- **Top differential diagnoses** – AD, other dementing diseases, normal aging.
- **Prognosis** – Amnestic MCI evolves to AD (10–15 % per year); non-amnestic MCI can progress to dementing disorders other than AD.

16.4.1 Terminology and Definitions

This term originally referred to a transitional zone in subjects with memory complaints but without any evidence of functional decline. These subjects, although not fulfilling criteria for dementia, are at risk of developing AD or other dementing disorders. Although other subtypes of MCI have been described later, the most typical is characterized by memory impairment but with all other cognitive domains essentially spared (amnestic MCI). The original clinical criteria for MCI were: (a) memory complaint, preferably corroborated by an informant; (b) objective memory impairment for age; (c) essentially normal general cognition; (d) largely intact activities of daily living; (e) absence of dementia [11]. However, any single cognitive domain other than memory (non-amnestic MCI single domain) or multiple domains simultaneously (amnestic or non amnestic-MCI multiple domain) can be affected.

16.4.2 Prognosis

It is commonly believed that amnestic MCI typically evolves to AD, while non-amnestic MCI progresses to dementing disorders other than AD. However, each form of MCI is highly heterogeneous, with many MCI subjects who actually do not progress to dementia, but stop declining or even improve. Despite this variability in clinical outcomes, it is undisputed that MCI altogether represents an "at risk" condition, as indicated by the fact that, compared to normal elderly adults, those with amnestic MCI are more likely to evolve

to AD (10–15 % vs. 1–2 % per year) [11]. Predictors of conversion to AD include particularly bad performances on measures of delayed recall, presence of apolipoprotein epsilon 4 allele, hippocampal atrophy on cerebral MRI, parietal and temporal hypometabolism on FDG-PET, and low Abeta 42/high t-tau proteins in CSF.

16.4.3 Therapy

There is insufficient evidence that drugs used in dementia due to AD, including cholinesterase inhibitors, affect progression to dementia or cognitive test scores in MCI.

16.5 Dementia with Lewy Bodies (DLB)

Key Facts

- **Terminology and definitions** – Senile dementia of Lewy body type or Lewy body variant of Alzheimer disease.
- **Clinical features** – Visual hallucinations, parkinsonism, cognitive fluctuations, neuroleptic hypersensitivity.
- **Diagnostic markers**
  - **CSF** – Decrease of Abeta 42 protein and increase of phosphorylated and total tau (but lower than in AD). Genetics ns.
  - **MRI** – Hippocampal and medial temporal lobe atrophy, but lower than in AD.
  - **PET and SPECT** – occipital hypoperfusion/hypometabolism.
  - **MIBG – Myocardial scintigraphy** – Reduction of tracer retention.
  - **DAT scan** – Reduction of tracer retention in basal ganglia.
- **Top differential diagnoses** – AD, FTD, VaD, CJD
- **Prognosis** – Mean survival 7 years (range 2–20 years).
  - **Principles of treatment** – Low doses of levodopa; traditional neuroleptics should be avoided.

16.5.1 Terminology and Definitions

Also previously known as senile dementia of Lewy body type or the Lewy body variant of Alzheimer disease, DLB has been reported to be the second most common form of degenerative dementia, after AD. While nigral Lewy bodies (LBs) have traditionally been associated with Parkinson disease, cortical LBs have recently been recognized as potential neuropathological substrates of dementia. The importance of identifying this entity lies essentially in its pharmacological management, with a potential good response to cholinesterase inhibitors, but increased sensitivity to adverse effects of neuroleptic drugs.

In addition to cognitive decline, the core clinical features of DLB [12] are visual hallucinations (VHs), which typically are recurrent, well-formed, and detailed; fluctuating cognition with pronounced variations in attention and alertness; and spontaneous (i.e., not drug-induced) features of parkinsonism, with an overrepresentation of the "postural instability-gait difficulty" phenotype. In general, the accuracy for the clinical diagnosis of DLB using the criteria originally suggested by the Consortium on DLB [12] has not been satisfactory, essentially due to the suboptimal sensitivity of the criteria. To improve diagnostic accuracy, a substantial weight has more recently been given to REM behavior disorder (RBD), neuroleptic hypersensitivity, and decreased striatal binding at presynaptic dopamine transporter sites [13].

16.5.2 Diagnostic Markers

CSF Phosphorylated and total tau are in general lower in DLB than AD. Conversely, Abeta 42 is usually comparable, reflecting high plaque deposition in both DLB and AD.

MRI Hippocampal and medial temporal lobe atrophy is less pronounced in DLB than AD. This is in keeping with autopsy findings but, in early-stage dementia, preservation of medial temporal lobe volumes may be seen in both diseases.

SPECT and PET Occipital hypoperfusion/hypometabolism is more frequently associated to DLB than AD. However, these abnormalities are seen in only approximately 50–70 % of DLB cases (suboptimal sensitivity) and their specificity has recently come into question. [I-123] MIBG myocardial scintigraphy has been reported to be significantly superior to brain perfusion SPECT in the identification of DLB subjects. MIBG scintigraphy enables quantification of post-ganglionic sympathetic cardiac innervation (see Chap. 36). Decreased tracer retention in the myocardium has been reported in DLB, but not in AD. As mentioned, striatal binding at pre-synaptic dopamine transporter sites is more reduced in DLB than AD.

Pathology Pathological diagnosis of DLB requires the presence of Lewy bodies (LBs), but also permits other pathologies, including Alzheimer changes in the form of plaques and tangles. A cerebral biopsy is usually not performed for diagnostic purposes. Of note, the presence and severity of concurrent AD pathology in DLB modifies the clinical presentation, with decreased rates of VHs and parkinsonism as neurofibrillary tangle pathology increases, making these cases harder to recognize.

16.5.3 Top Differential Diagnosis

AD, FTD, VaD, CJD, metabolic, infectious, toxic, alcoholic encephalopathies.

16.5.4 Therapy

Three categories of symptomatology are central to DLB: cognitive impairment, neuropsychiatric features, and motor dysfunction. Unluckily, treatment of motor dysfunction may exacerbate neuropsychiatric symptoms and that of neuropsychiatric symptoms may exacerbate motor dysfunction. When significant parkinsonism is present, the challenge for the clinician is to improve it without exacerbating psychotic symptoms (especially visual hallucinations), hypersomnolence, and orthostatic hypotension. Thus, the lowest effective dose of levodopa should be used. Dopamine agonists are usually not recommended. Visual hallucinations, a core feature of DLB, are usually recurrent but not frightening. Thus, their treatment is rarely necessary and, in any case, the traditional neuroleptics should be avoided because of the potential risk of severe adverse effects [13]. If necessary, the newer atypical antipsychotics can be used at the lowest effective dose. In a 5-month study of rivastigmine for DLB, there was a greater benefit on behavioral than cognitive symptoms [14]. In a 3-month study of donepezil, there was a significant benefit on both cognitive and behavioral symptoms [15]. Memantine may be another option for patients with DLB, but the effects of this drug seems to be extremely modest.

16.5.5 Prognosis

The average survival for persons with DLB after the appearance of the first symptoms is 7 years. However, the range is extremely wide (2–20 years), depending on age at onset, symptom severity, and concurrent medical conditions. The presence of parkinsonism has a negative influence on survival [16]. Patients with DLB have been reported to have an increased mortality risk [HR 1.88 (CI 1.4–2.05)] and a shorter survival (78 vs. 86.6 years; $p = 0.001$) compared to patients with AD [16]. However, there is conflicting evidence as to whether DLB and AD patients differ in the rate of cognitive decline, with some studies failing to observe any differences [16] and others documenting a faster cognitive decline (5.8 vs. 4.1 points/year on the Mini Mental State Examination) in DLB patients than in those with AD [17]. Compared to AD,

DLB patients may also have a greater risk of institutionalization and an earlier time to nursing home placement [16]. In a longitudinal study of 43 individuals with mild DLB in western Norway, the median time until nursing home placement was 663 days (range = 342–984 days) [18]. The use of cholinesterase inhibitors was associated with delayed institutionalization (hazard ratio [HR] 0.24 [0.70, 0.82]), whereas the use of antipsychotic medication was associated with a markedly increased rate of nursing home admission (HR 37.3 [4.35, 320, 64]). Like AD, DLB evolves into severe dementia and eventually impairs the person's ability to speak or move. The most common cause of death is pneumonia or other primary infection, which is usually induced by dysphagia, inhaling food or drink into the airway, from a catheter inserted into the body, and/or from becoming bedridden.

16.6 Frontotemporal Dementia (FTD)

Key Facts

- **Terminology and definitions** – Pick disease, frontal lobe dementia, frontotemporal dementia
- **Clinical features** – Heterogeneous behavioral abnormalities, executive and language functions primarily impaired.
  - **Clinical subtypes**: bvFTD, PNFA, PFA frontotemporal dementia, semantic dementia, nonfluent aphasia, FTD with associated motor neuron disease (FTD-MND), corticobasal degeneration, and progressive supranuclear palsy.
- **Diagnostic markers**
  - **Neuropathology** – Tau-positive inclusions, or tau-negative but TDP-43-positive inclusions
    - **CSF** – Total tau (T-Tau) and/or phosphorylated tau (P- Tau) or Tau/Aβ42 or P-Tau/Aβ42 ratios may assist in differentiating FTD from AD
    - **Genetics** – FTD is autosomal dominant (40 % of cases); Mutations in progranulin or MAPT gene; chromosome 9 open reading frame 72 (C9ORF72) is associated especially with bvFTD
    - **MR** – Frontal and temporal lobes atrophy
    - **^{18}FDG-PET** – Reduction of glucose metabolism in the frontal and temporal regions
- **Top differential diagnoses** – MCI, AD, DLB, VaD, CJD, secondary dementias
- **Prognosis** – Median survival 6 ± 1.1 years (bvFTD); 3 ± 0.4 years (FTD-MND). Survival rarely exceeds 10–12 years from the onset
- **Principles of treatment** – Symptomatic

16.6.1 Terminology and Definitions

The term FTD refers to multiple, heterogeneous, clinical conditions resulting from degeneration of frontal and/or temporal lobes.

16.6.2 Clinical Features

Demographics Altogether, they represent less than 10 % of all dementias in the elderly, but up to 50 % of cases below age 60.

In FTD, frontal and/or temporal cortices are often selectively involved with clinical syndromes essentially characterized by behavioral abnormalities, executive dysfunction, and language deficits.

The clinical spectrum of FTD includes the behavioral variant of FTD (bvFTD), progressive non-fluent aphasia (PNFA), and progressive fluent aphasia. The latter usually evolves into semantic dementia (SD), a term that implies the further development of deficits such as visual agnosia in addition to fluent aphasia. Other clinical conditions associated with FTD include motor neuron disease (FTD-MND or FTD-ALS), corticobasal degeneration, and progressive supranuclear palsy. The cardinal clinical features of corticobasal degeneration include progressive asymmetric rigidity and apraxia, with other symptoms and

signs suggesting additional cortical (e.g., alien limb phenomena, cortical sensory loss, myoclonus, mirror movements) and basal ganglionic (e.g., bradykinesia, dystonia, tremor) dysfunction.

The typical presentation of progressive supranuclear palsy includes supranuclear gaze palsy, falls due to postural instability, and parkinsonism. However, both corticobasal degeneration and progressive supranuclear palsy may develop with no gaze palsy, parkinsonism, or gait impairment, but with primary progressive aphasia, apraxia of speech, or frontotemporal dementia.

Pathology Neuropathologically, FTD is also very heterogeneous, but the predominant subtypes are two, the former characterized by tau-positive inclusions, the latter characterized by tau-negative but TDP-43-positive inclusions.

Clinical features in relation to pathology Like AD, bvFTD is characterized by an insidious onset and gradual progression but, as opposed to AD, usually appears at earlier ages and presents with early decline in social interpersonal conduct, early emotional blunting, loss of empathy, apathy, early loss of insight, selfishness, and neglect of personal hygiene. Although the structure of language (syntax, morphology, and semantics) is usually unimpaired, there may be early reduction of speech output and stereotypy of speech. Frontal (right more than left) lobes and/or anterior temporal lobes are selectively involved.

PNFA also develops insidiously and evolves gradually and, by definition, is initially characterized by cognitive deficits restricted to language functions. Spontaneous speech is not fluent and is characterized by at least one among agrammatism, phonemic paraphasias, and anomias. Apraxia of speech (effortful speech, difficulty in initiating speech, abnormal intonation, and articulation) is often associated. Behavioral changes are not prominent and usually late. The left anterior perisylvian region is selectively involved.

In SD, the language disorder is characterized by progressive, fluent, empty spontaneous speech (Wernicke-like aphasia). Loss of word meaning usually precedes visual agnosia. There is typically an asymmetric abnormality predominantly affecting the dominant (left) anterior temporal lobe. These conditions (bvFTD, PNFA, and SD) may all include extrapyramidal symptoms and variably overlap with motor neuron disease, and corticobasal and progressive supranuclear syndromes. However, extrapyramidal and motor neuron signs are rarely found in SD.

Motor neuron disease in FTD may include both pyramidal tract degeneration and anterior horn cell disease. Affected individuals usually present with cognitive and behavioral changes, but weakness, fasciculations, muscle atrophy, bulbar symptoms such as dysarthria and dysphagia, may all precede or coincide with cognitive symptoms. Of all subjects with FTD, approximately 50 % have an abnormal accumulation of TDP-43, a protein implicated in DNA transcription and alternative splicing, about 40 % have an abnormal accumulation of protein tau, and the remaining have an abnormal accumulation of other proteins. However, while an abnormal TDP-43 deposition can be found in any of the FTD syndromes (bvFTD, PNFA, SD, FTD-MND), an abnormal tau deposition can commonly be found in bvFTD and PNFA, but not in SD and FTD-MND.

Clinical features in relation to genetics Approximately 40 % of patients with FTD have dementia, following an autosomal dominant pattern of inheritance. Mutations have been identified in five genes, although most of the identified mutations are in the progranulin gene (PGRN) or the MAPT gene on chromosome 17. The most recently identified gene associated with FTD, and especially with bvFTD, is chromosome 9 open reading frame 72 (C9ORF72), whose mutation (an intronic hexanucleotide repeat expansion of GGGGCC) also accounts for a high proportion of familial ALS cases.

For individuals with familiar FTD associated with mutations in the MAPT gene, the penetrance is complete and the age at onset is usually between 30 and 60 years. Behavioral abnormalities and executive dysfunction with varying degrees of parkinsonism and aphasia develop in many but symptoms such as memory impairment, visuospatial impairment, and apraxia, which are relatively common in individuals with mutations in

the progranulin gene and reflect the involvement of parietal, in addition to frontal and temporal regions, are rare. Cerebral atrophy in progranulin mutation carriers is also more asymmetric than in individuals with MAPT or C9ORF72 mutations.

16.6.3 Diagnostic Markers

CSF total tau (T-Tau) and/or phosphorylated tau (P-Tau) or Tau/Aβ42 or P-Tau/Aβ42 ratios may assist in differentiating FTD from AD.

CT or MRI can demonstrate prominent, sometimes asymmetric, atrophy of the frontal and temporal lobes in FTD (Figs. 16.2 and 16.3).

Functional neuroimaging (PET or SPECT) may be quite useful in differentiating FTD from AD and other dementias.

16.6.4 Top Differential Diagnosis

MCI, AD, DLB, VaD, CJD, metabolic, infectious, toxic, alcoholic encephalopathies, psychiatric disorders.

16.6.5 Prognosis

Therapy To date, there is no evidence of efficacy for either memantine or cholinesterase inhibitors on cognitive symptoms of FTD which, unlike AD and DLB, are not characterized by cholinergic dysfunction. Cholinesterase inhibitors should be avoided because they may increase irritability. Since patients with FTD have a presynaptic serotoninergic deficit, selective serotonin reuptake inhibitors have been used in the past with little benefit on irritability, overeating, and repetitive compulsive behaviors. Currently, pharmacological intervention in FTD is essentially aimed at symptomatic improvement of psychiatric and behavioral symptoms.

Prognosis A few people with FTD can live for a very long period of time, while others progress more rapidly. As expected, those who develop extrapyramidal or, especially, pyramidal signs associated to MND, have a much faster rate of progression. Although the average survival from diagnosis is 3–10 years, life expectancy is influenced by several clinical variables, including use (and abuse) of antipsychotics and quality of care. In a clinico-pathological study of 61 patients in which all subtypes of FTD were represented [19], the median survival was 6 ± 1.1 years for bvFTD and 3 ± 0.4 years for FTD-MND. However, survival across bvFTD, semantic dementia, progressive non-fluent aphasia, and corticobasal degeneration subjects was similar, implying that, within the spectrum of FTD, FTD-MND is by far the most malignant disorder. Interestingly, when analyses were performed stratifying the patients into two groups according to the pathological

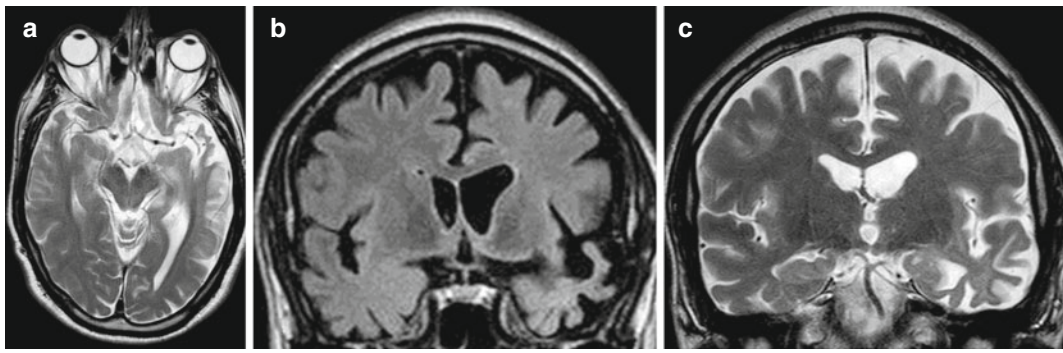

Fig. 16.2 Fronto-temporal dementia (FTD), temporal variant. Axial and coronal T2-weighted images (**a**, **c**), and coronal FLAIR image (**b**) demonstrate marked atrophy of the left temporal lobe associated with white matter abnormal signal intensity. Note the mild enlargement of the frontal and temporal horns

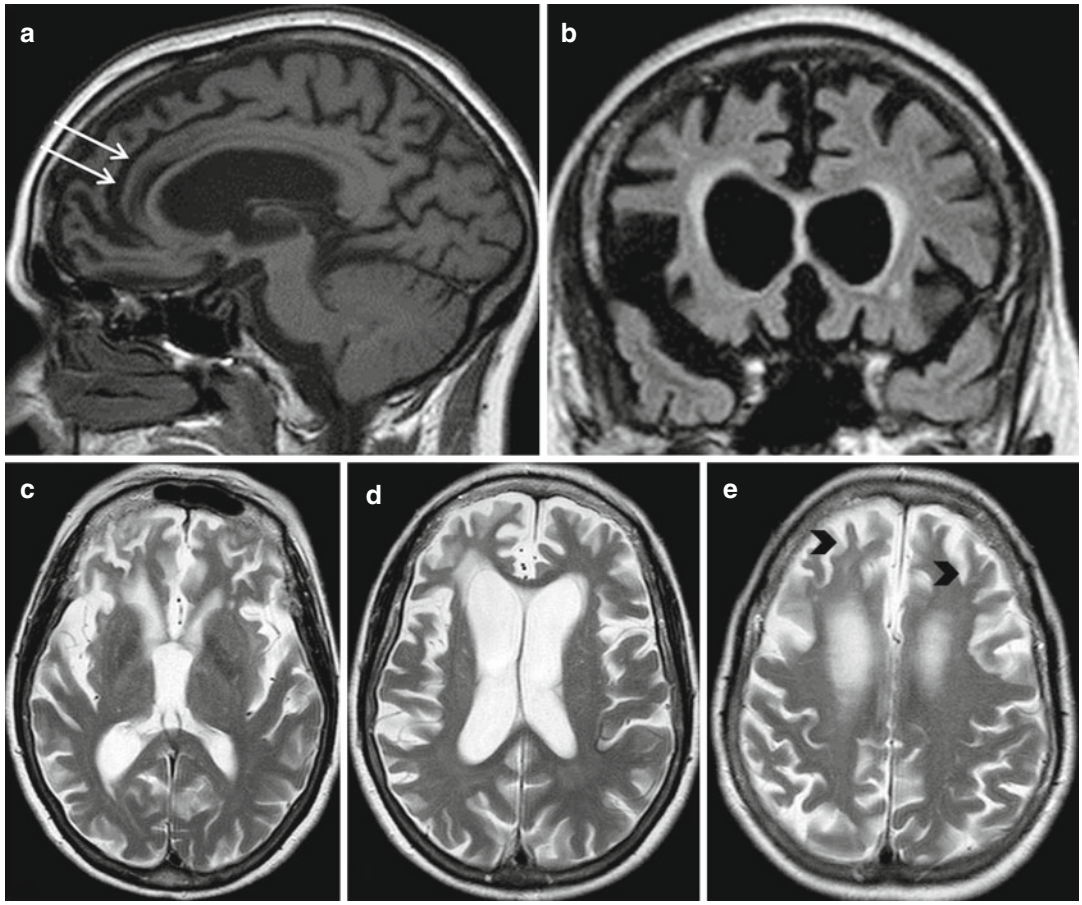

Fig. 16.3 Fronto-temporal dementia (FTD), frontal variant. Sagittal T1-weighted image (**a**) shows frontal cortical atrophy with marked thinning of the anterior portion of the cingular gyrus (*arrows*). Coronal FLAIR and axial T2-weighted images (**b**–**e**) demonstrate diffuse cerebral atrophy, mainly in the frontal lobes and in the insular regions; the thinning gyri are similar to a "knife blade", *arrowheads* in (**e**). Enlargement of the ventricles are especially visible in the frontal horns. Note the white matter slight hyperintensity in both frontal lobes, while precentral gyrus is relative spared

substrate (tau-positive vs. tau-negative pathology), cases with tau-negative pathology, which included those with FTD-MND, had a significantly worse prognosis (median survival 5.0 vs. 9.0) despite a younger age at onset. In another study [20], survival and rates of cognitive and functional decline were compared between autopsy-confirmed FTD and AD patients, matched for age, education and MMSE score at initial evaluation. The former had significantly shorter survival from initial evaluation to death (4.2 vs. 6.0 years) and declined significantly faster over 1 year on the MMSE (mean annual rate of change: −6.7 points for FTD vs. −2.3 points for AD). Notably, bv-FTD was the most represented in the FTD sample. A significantly greater proportion of patients with FTD were impaired in basic activities of daily living at initial evaluation and lost the capacity for independent or minimally assisted ADLs over the subsequent year.

Prognosis is also affected by genetics. In fact, compared to individuals with mutations in the MAPT gene, those with mutations in the progranulin gene tend to have a later age at onset (45–85 years) and a more variable and often longer duration of illness (1–15 versus 3–10 years).

Whatever the initial clinical subtype, FTD individuals eventually experience difficulties in

chewing, swallowing, moving, and controlling their bladder and bowel. As for AD, death from FTD is determined by the consequences of these physical changes, resulting most commonly from lung, skin, or urinary tract infections. Survival, although extremely variable, rarely exceeds 10–12 years from the appearance of first symptoms. Nonetheless, some patients may exceptionally live for 20 years.

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Intellectual Disability

17

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Abbreviations

AS, Angelmann syndrome; CNS, central nervous system; DD, developmental delay; DS, Down syndrome; ELN, elastin; FAS, fetal alcohol syndrome; FMR1, Fragile X mental retardation 1; ID, intellectual disability; IQR, interquartile range; MR, mental retardation; SMR, standardized mortality ratios; VCFS, Velo-cardio-facial syndrome

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Key Facts

- **Terminology and definitions** – ID is a "significant limitation *both* in intellectual functioning and in adaptive behavior." Its onset is before 18 years of age and IQ score is less than 70
- **Clinical features** – Prevalence of ID is 1–2 %. ID may be mild (IQ = 50–70) (85 % of the mentally disabled), moderate (IQ = 30–49) (10 % of the ID), severe (IQ = 20–29) (3–4 % of the ID) or profound (IQ < 20) (1–2 % of the ID). ID may be associated dysmorphisms and behavioral disorders
- **Diagnostic markers**
  - **Clinical** – Often complex clinical syndromes and constellations
  - **Blood** – Targeted screening (hypothyroidism, fetal alcohol syndrome, etc.)
  - **CSF** – Targeted screening
  - **Genetic** – *Karyotype* studies is abnormal in 4 %, *microarray analysis* is abnormal 7.8 % of pts. *Mutations of X-linked genes* may diagnose up to 10 % of ID
  - **Imaging**
    CT – Diagnostic in 30 % of patients
    MRI – Diagnostic in 48.6–65.5 % of patients
  - **Neurophysiology** – *EEG* – For epileptic syndromes
- **Top differential diagnoses** – Childhood illnesses or injuries, hereditary disorders, infection, inborn errors of metabolism, and poisoning
- **Prognosis**
  - **Principles of treatment** – Treatment is most often supportive
  - **Disability** – Median age of death decreases with the decrease of IQ.
  - **Mild ID** – Patients can become self-sufficient and in some cases live independently, with family support (median age of death = 68 years). *Moderate ID* – Can work and perform self-care tasks with moderate supervision (median age of death = 64 years). *Severe ID* – May acquire very basic self-care and some communication skills (median age of death = 59 years). Profound ID needs a high level of assistance (median age of death = 46 years)

17.1 Terminology and Definitions

The condition currently defined as "mental retardation" (MR) comprises a cluster of disorders characterized by low intelligence and limitations in adaptive behavior [1].

The disorder "Iintellectual disability" (ID) is defined as "significant limitations *both* in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills." This disability originates before age 18 years and has widely replaced MR for policy, administrative and legislative purposes.

In early infancy, and in the first 5 years of life in particular, the condition termed *developmental delay* (DD) affects 5–10 % of children, and defines a clinical condition coinciding with a performance of at least 2 standard deviations below the mean for chronological age in at least two of the following areas: (1) global and fine motor control, (2) language, (3) cognition, (4) personal/social relationships, and (5) activities of daily living [2].

The severity of ID can be classified on the basis of the intelligence quotient (IQ) measured by standardized tests. Scores below 70 (2 standard deviations below the mean) represent the cut-off in identifying intellectually disabled individuals. ID can be distinguished as mild (IQ 50–70) (85 % of the mentally disabled), moderate (IQ 30–49) (10 % of the mentally disabled), severe (IQ 20–29) (3–4 % of the mentally disabled) or profound (IQ <20) (1–2 % of the mentally disabled) [1, 3].

IDs have a major impact on functioning and disability throughout the life course, and high comorbidity with other cognitive disorders. Frequently misdiagnosed, ID is associated with poor access to health care services and involves very high costs for the health care system and for society as a whole [4].

17.2 Epidemiology

ID is the most common developmental disorder. Its prevalence is around 1 % in high income countries and 2 % in low and middle income countries. On average, about 1 % of children aged from 3 to 10 years have ID. ID is more frequent in older children (ages 6–10 years) than in

younger children (ages 3–5 years). ID is also more common in boys than in girls and in black than in white children. Mild ID accounts for 85 % of the mentally disabled, moderate ID for 10 %, severe ID for 3–4 %, and profound ID for 1–2 % of the mentally disabled [5, 6].

17.3 Clinical Features

Infants and children who have ID generally do not reach developmental milestones within the expected age range (e.g., sitting up, crawling or walking, talking or using coherent language). They also have other symptoms of cognitive impairment such as deficits in short-term memory, concept formation, understanding social rules, problems solving, and understanding cause and effect relationships [1].

17.4 Diagnosis

Genetic syndromes (alias dysmorphic-genetic syndromes) are complex pathological constellations in which genetic abnormalities are often associated with mild to severe dysmorphisms, psychomotor delay, mental retardation, and behavioral disorders. They can be secondary to chromosomal abnormalities, numerical or structural, or to single gene mutations. Often, the underlying abnormality is unknown and diagnosis may be based exclusively on clinical data remembering that

1. The presence of a single minor abnormality cannot be deemed to have clinical significance
2. At least three typical features are needed for a correct diagnosis
3. The collection of photographic evidence is useful for reassessing a patient over time
4. Each diagnostic hypothesis can be assessed with the help of computerized systems (Possum database, London Dysmorphology) [1, 2]

Common causes of ID are

1. Genetic conditions (fragile X syndrome, Down syndrome, inborn errors of metabolism)
2. Pathogenic noxae during pregnancy or birth (e.g., congenital cytomegalovirus, fetal alcohol syndrome [FAS], etc.)
3. Anomalies affecting CNS at birth or soon after (e.g., hydrocephalus, asphyxia, etc.)
4. CNS syndromes (e.g., stroke, infections, traumas, etc.) during infancy, childhood, and adolescence

Many causes of ID can be prevented or appropriately treated after birth.

Thirty to forty percent of mental retardation is associated with dysmorphic-genetic syndromes that can be secondary to chromosomal abnormalities or gene mutations.

17.5 Clinical Markers

Blood – Targeted screening

Neuropsychological tests – Severity ID/DD is ascertained by means of neuropsychological tests: Griffiths Mental Developmental 0–2, and 2–8 years, Wechsler Scales (WPPSI, WISC III or WISC IV), Leiter-R test, and others.

Genetic – Karyotype studies are abnormal in at least 4 % of subjects with ID and in 18.6 % of patients with syndromic features [7].

Chromosomal microarray analysis (CMA) or microarray-based comparative genomic hybridization according to clinical phenotypes. Microarray testing is abnormal in 7.8 % of subjects with ID and in 10.6 % of patients with syndromic features [8, 9].

Mutations of X-linked genes may be diagnosed in up to 10 % of ID. Testing of XLID genes has a yield of 42 % in males from definitely X-linked families and of 17 % in males from possibly X-linked families. *FMR1* testing has a combined yield of at least 2 % in male and female subjects with mild ID. *MeCP2* mutations are found in 1.5 % of girls with moderate/severe ID and in less than 0.5 % of males with ID.

CT – Contributes to the etiological diagnosis of intellectual disability in approximately 30 % of patients (Class III studies).

MRI – Demonstrates abnormalities in 48.6–65.5 % of patients with global delay. The chance of positive results increases if clinical deficits are also present.

EEG – Suggests the presence of epilepsy and specific epileptic syndrome.

Top differential diagnoses – Childhood illnesses or injuries, hereditary disorders, infection, inborn errors of metabolism, and poisoning, etc.

17.6 Prognosis

17.6.1 Principles of Treatment

Treatment is most often supportive. With improved understanding of genetic and cellular mechanisms, novel treatment options are beginning to appear for a number of specific conditions. Fragile X and tuberous sclerosis offer paradigms for the development of targeted therapeutics, but advances in understanding of other disorders, such as Down and Rett syndromes, are also offering encouraging treatment directions.

In addition, better understanding of the underlying neurobiology is leading to novel developments in enzyme replacement for storage disorders and adjunctive therapies for metabolic disorders.

17.6.2 Disability and Mortality

Patients with developmental disabilities are at increased risk for behavioral and psychopathological disorders that impact on individuals, family functioning, and possibly on the wider community. For individuals, it is associated with reduced vocational, social and occupational opportunities, restricted participation in educational and recreational programs, and problematic placement in factories for disabled workers or even in residential communities. Child behavioral problems are associated with high ratings of parent stress and depressive symptoms. Moreover, the higher the ratings of behavioral and emotional disturbances in the child, the greater are the direct and indirect financial costs of care to parents.

Left untreated, behavioral problems in children with developmental disabilities are likely to persist, with evidence of only a small decline in the levels of emotional and conduct problems as children move into young adulthood [10].

People with ID experience a variety of health inequalities compared with the general population. They are more likely to die younger. Many studies have observed substantially higher standardized mortality ratios (SMR) in people with ID than in the general population, but the magnitude of these differences differed considerably. Much of the excess mortality in the ID population occurs in younger people (under the age of 40 years). People with more severe ID have particular disadvantage; an SMR of 8.4 has been reported in children and adolescents with moderate to profound ID compared with 1.4 for those with mild ID. The risk of dying at an early age was greatest for people with more severe intellectual disabilities, but the median age at death of people with mild intellectual disabilities (68 years) was still substantially younger than in the general population. Factors found to increase premature mortality in this population are a greater number of disabilities, reduced mobility, presence of epilepsy, presence of cerebral palsy, or presence of Down syndrome [11, 12]

17.6.3 Mild Mental Retardation (IQ 50–70)

Individuals with mild ID may have problems in reaching developmental milestones and acquiring language. With adequate training, most of these people will achieve full independence in most domains of function but may have some problems with adaptive integrative domain.

Most problems occur when they are matriculating through the educational system and developing interpersonal relationship skills with peers. Job coaches or aides may be necessary to help them in work routines and to develop solid employment skills. Most individuals (87 %) with mild ID will exhibit barely noticeable problems of learning; however, as the demands of academic

work become more complex, differences will appear more pronounced.

Median age of death is inversely proportional to the severity of intellectual impairment and decreases when the intellectual disability is more pronounced. In mild ID, the median age of death is 68 years (IQR 58–77) [10].

17.6.4 Moderate Mental Retardation (IQ 30–50)

In addition to the deficits and needs of the above people, patients with moderate mental retardation may have additional insufficiencies in language expression and comprehension. They will need guidance and support throughout their lives. Their academic skills will always be limited and may not develop beyond a basic level.

Semi-independent living conditions are usually best and safest. They will need close supervision in employment endeavors but can be very dependable and loyal workers if given the appropriate structured tasks, training, and support. They can develop simple friendships and engage in appropriately supervised and developed physical activities. In moderate retardation, the median age of death is 64 years (IQR 52–75) [10].

17.6.5 Severe Mental Retardation (IQ 20–29)

As the degree of functioning decreases, the amount of needed support and supervision increases. Limitations in expected levels of achievement also increase. Problems with marked degrees of motor impairment or other associated deficits are prevalent. Clinically significant damage to or maldevelopment of the CNS is also a negative factor. These patients will need care and supervision to perform most activities of daily living. In severe retardation, the median age of death is 59 years (IQR 31–72) [10].

17.6.6 Profound Mental Retardation (IQ <20)

People with symptoms or behaviors that meet criteria for profound ID have severe limitations (rudimentary level) in language comprehension, expression, and ability to comply with requests or instructions. They are primarily deprived or severely restricted in mobility, are incontinent, and require constant help and supervision. Expectations for attaining developmental milestones and matriculating through infancy, childhood, and adolescence to adulthood are severely limited. In profound retardation, the median age of death is 46 years (IQR 41–68) [10].

17.7 Prognosis of the Main Intellectual Disability

17.7.1 Fragile X Syndrome (FMR1)

Key Facts

- **Terminology and definitions** – Fragile X syndrome is an X-linked dominant cause of intellectual disability with a prevalence of 1/2000–1/3000 live births.
- **Clinical features** – Moderate ID (IQ 30–50), psychomotor retardation, behavioral disorders, craniofacial dysmorphisms with long face, prominent forehead, large or prominent ears, and prognathism.
- **Diagnostic markers**
  - **Genetics** – People with fragile X syndrome full mutation have over 200 CCG FMR1 repeats of gene on chromosome X (X q27.3).
  - **Imaging** – *Brain MRI* – Can disclose cerebellar vermis hypoplasia and increased volume of hippocampus.
- **Top differential diagnoses** – Other causes of ID
- **Prognosis.**
  - **Treatment** – Supportive.
  - **Disability** – Patients with Fragile X syndrome have normal life expectancy.

17.7.1.1 Definition

Fragile X syndrome is an X-linked dominant cause of intellectual disability caused by FMR1 (Fragile X mental retardation 1) gene mutation on chromosome X (X q27.3). The mutation is associated with an expansion of CGG repeats, which determines a deficit of FMR1-protein.

17.7.1.2 Epidemiology

Prevalence is 1/2000–1/3000 live births. FMR1 is the only gene associated with fragile X syndrome.

17.7.1.3 Clinical Features

Intellectual disability is moderate (IQ 30–50). In fully mutated (hemizygotes) males, the prepubertal clinical picture is characterized by psychomotor retardation, commonly affecting language, often associated with behavioral disorders, cranio-facial dysmorphisms with long face, prominent forehead, large or prominent ears, and prognathism.

Some patients present some or all the symptoms of autism. In a series of 27 fragile X children, 8 % fulfilled the diagnostic criteria for autism. On the other hand, the incidence of fragile X syndrome in autistic patients is 2.5–6 %. However, unlike severely impaired autistic children, fragile X children maintain the ability to recognize human facial expressions of emotion.

Epilepsy with onset in early infancy is present in 20 % of patients. Seizures generally respond to common antiepileptics and tend to vanish over time until disappearance in adolescence, although they occasionally persist until adulthood.

The main postpubertal phenotypic characteristics of FMR1 are given by macrocrania, strabismus, prognathism, macroorchidism, joint hyperextensibility, subluxation of the thumb, and flat foot.

The behavioral disorders include hyperactivity and social anxiety, obsessive-compulsive conditions, and psychotic symptoms. Mitral valve prolapse has been observed in 50 % of adults.

Females with full mutation (heterozygotes) show similar, less severe physical and behavioral characteristics.

Premutation patients generally have a normal appearance and intelligence. Some may present slight cognitive or behavioral disorders: learning difficulty, social anxiety.

Finally, another disorder, characterized by less severe mental delay and less marked somatic traits, has been described in males with expansion of CCG repeats in the FRAXE fragile site (clearly distinct from FRAXA, the fragile site associated with the more common fragile X syndrome) in the FMR2 gene. Given that mutations in FRAXE are far less common, routine testing in subjects with mental retardation is not deemed opportune [13].

17.7.1.4 Diagnostic Markers

Genetic – Genetic tests focus on the number of CGG repeats on FMR1 gene that normally contains fewer than 44 trinucleotide repeats. Fragile X syndrome shows a clear genotype-phenotype correlation. Premutation carriers have about 55–200 trinucleotide repeats. People with fragile X syndrome full mutation display over 200 repeats.

Brain MRI – Can disclose cerebellar vermis hypoplasia and, more rarely, increased volume of hippocampus, caudate nucleus, and thalamus [14].

17.7.1.5 Prognosis

Life expectancy for patients with FRM1 is nearly normal. As usual, quality of life depends on the amount of intellectual disability. Recurrent infections in children and seizures are possible complications.

17.7.2 Angelman Syndrome (AS)

Key Facts

- **Terminology and definitions** – Angelman syndrome is a neurogenetic disorder most commonly associated with a deletion of the maternal chromosome 15q11-13.
- **Clinical features** – Prevalence of Angelman is 1/12,000.
  Severe psychomotor retardation and gait ataxia with impairment of language are characteristic.
- **Diagnostic markers**
  - **Laboratory**
    - **Genetics** – Maternal chromosome 15q11-13 deletion. Paternal disomy (3–5 % of cases).
    - **Imaging** – *Brain MRI* – Microcephaly, mild cortical atrophy, and ventriculomegaly, thin corpus callosum.
    - **Neurophysiology** – *EEG* – High-amplitude slow-wave activities prominent in the frontal region and spike-and-slow-wave multifocal activity.
- **Top differential diagnoses** – Others IDs.
- **Prognosis**
  - **Principles of treatment** – Supportive.
  - **Disability** – Chiefly dependent on severity of ID.

17.7.2.1 Definition

Angelman syndrome (AS) is a neurogenetic disorder most commonly associated with a deletion of the maternal chromosome 15 (15q11-13). In 3–5 % of cases, Angelman is due to paternal uniparental disomy (both the alleles are inherited from the father). In 4–6 % of cases, it is caused by an imprinting centre defect or to E6-P ubiquitin-protein ligase (UBE3A) gene mutations.

The 15q11-13 region contains the genes for the main inhibitory neurotransmitter system, the β3, α5, and γ3 subunits of the r gamma-aminobutyric acid type-A receptor (GABA(A) R). A link between the β3 subunit gene and susceptibility to autism has been suggested. In 20 % of cases, no genetic abnormality is demonstrated and the diagnosis remains clinical.

17.7.2.2 Epidemiology and Clinical Features

The prevalence of Angelman is estimated 1/12,000.

Patients present severe psychomotor retardation and gait ataxia: gait is stiff, clumsy, and unsteady. Impairment of language, mainly expressive, is characteristic. Nonverbal performances can vary widely; some children learn sign language and alternative methods of social interaction.

A frank behavioral disorder represents a constant feature. Angelman children have been dubbed "happy puppets" on account of their manner; they are typically cheerful and excitable, hyperactive, and inattentive, a profile associated with stereotyped "hand fluttering."

More than 80 % of patients also present microcephaly, epilepsy with seizures often appearing after the age of three years. Deleted patients may often present drug-resistant atypical absence or myoclonic seizures. Less common signs (20–80 % of cases) include flat occiput, strabismus, macrostomia, widely spaced teeth, prominent jaw, and hypopigmentation of skin and eyes [15].

17.7.2.3 Diagnostic Markers

Genetic – Maternal chromosome 15 (15q11-13) deletion. Paternal disomy (3–5 % of cases). E6-P ubiquitin-protein ligase gene mutations.

Brain MRI – Microcephaly, mild cortical atrophy, and ventriculomegaly, thin corpus callosum. Occasionally cerebellar hypoplasia, unilateral temporal lobe hypoplasia, and vermian cysts may be found.

EEG pattern – High-amplitude slow-wave activities prominent in the frontal region and spike-and-slow-wave multifocal activity prominent in occipito-frontal areas.

17.7.2.4 Prognosis

Treatment is supportive. The severity of deficits is variable in AS and larger deletions on chromosome 15 are more disabling. Life span is near average.

17.7.3 Williams Syndrome

Key Facts	
• **Terminology and definitions** – Williams syndrome is an ID due to a submicroscopic deletion of chromosome 7 (7q11.23). • **Clinical features** – Prevalence is 1/10,000–1/20,000. Characteristic facial dysmorphisms, mental retardation, short stature, connective tissue abnormalities, distinctive typical behavior. Hypercalcemia in 15 % of patients. Cardiovascular disorders.	• **Diagnostic markers.** – **Genetics** – Submicroscopic deletion of chromosome 7 (7q11.23). – **Imaging** – *Brain MRI* – Reduced cerebral volume may be observed. • **Top differential diagnoses** – Others IDs. • **Prognosis** – **Principles of treatment** – Supportive. – **Disability** – Chiefly dependent on severity of ID.

17.7.3.1 Definition

Williams syndrome is an intellectual disability due to a submicroscopic deletion of chromosome 7 (7q11.23); the deleted region spans approximately 1.5 megabases and contains 14 genes. Many of the clinical manifestations are caused by a deletion of the elastin gene, which results in abnormal elastin (ELN) production and consequent connective tissue alterations. LIM kinase 1 (LIMK1), a gene contiguous to ELN, is the second gene implicated in the syndrome. In particular, the cognitive profile of the syndrome seems to be attributable to the deletion of LIMK1 gene expressed in the brain and probably involved in the development of neural pathways responsible for visuospatial integration.

17.7.3.2 Epidemiology

The prevalence of this syndrome is between 1/10,000 and 1/20,000.

17.7.3.3 Clinical Features

Diagnosis is based on characteristic facial dysmorphisms, mental retardation, short stature, connective tissue abnormalities, a distinctive cognitive profile, and typical behavioral phenotype. Younger children present a broad forehead with bitemporal narrowing, periorbital oedema, stellate iris, strabismus, low-set nasal root, bulbous nasal tip, flattened cheekbones, prominent earlobes, long philtrum, wide mouth and full lips, patho-occlusion with small widely spaced teeth, and micrognathia.

Distinctive features in older children and adults are: (A) prominent supraorbital ridge, (B) narrowing of the nasal root, and (C) long neck.

Cardiovascular alterations constitute the main connective tissue abnormality with supravalvular aortic stenosis in most cases.

Idiopathic hypercalcaemia is observed in 15 % of patients.

Hypotonia is a further common early sign, and can be followed by spasticity and hyperreflexia.

Most affected subjects present mental retardation ranging from severe to, more often, mild.

Cognitive phenotype is extremely distinctive with high scores recorded on verbal subtests, exceeding IQ-based expectations, good scores on sentence repetition and memory tests, and lower-than-expected nonverbal scores.

Visuospatial organization and integration, writing and drawing are significantly impaired.

A high percentage of patients present attention disorders associated, or not, with hyperactivity and an excessively sociable and friendly

attitude to strangers. The incidence of behavioral problems (such as anxiety, worry, and attention deficit) and dependence is high [16].

Genetic – Submicroscopic deletion of chromosome 7 (7q11.23).

Brain MRI – Can reveal reduced cerebral volume and olygogyric microcephaly (author's personal observation). Sporadic cases show hyperplasia of the cerebellar vermis lobules VI–VII and VIII–XI or Chiari I malformation. Cerebrovascular accidents attributable to multiple intracranial arterial stenoses have been reported.

17.7.3.4 Prognosis

Treatment is supportive. As usual, quality of life disability and life expectancy (nearly normal) depend on the amount of intellectual impairment. Recurrent infections and seizures are possible complications.

17.7.4 Velo-Cardio-Facial Syndrome (VCFS)

Key Facts

- **Terminology and definitions** – Velo-cardio-facial syndrome (VCFS) (alias Di George sequence, CATCH 22, Shprintzen syndrome) is caused by a microdeletion of Chr 22q 11.2.
- **Clinical features** – Prevalence is 1/4000
  Involvement of the face, palate, and heart and, maybe, of other organs with marked phenotypic variability.
- **Diagnostic markers** – The association of palatoschisis with conotruncal cardiac defects in small children give rise to clinical suspicion.
  - **Laboratory**
    - **Genetics** – Chr 22q 11.2 microdeletion
    - **Imaging** – *Brain MR* – Structural abnormalities in the temporal and temporomesial regions.
  - **Neurophysiology**
- **Top differential diagnoses** – Others IDs.
- **Prognosis**
  - **Principles of treatment** – Supportive.
  - **Disability** – Chiefly dependent on severity of ID.

17.7.4.1 Definition

Velo-cardio-facial syndrome (VCFS) (alias Di George sequence, CATCH 22, Shprintzen syndrome) is caused by a microdeletion of Chr 22q 11.2 and characterized by involvement of the face, palate, and heart and, maybe, of other organs with marked phenotypic variability.

17.7.4.2 Clinical Features

Its prevalence is estimated to be around 1/4000.

More than 150 clinical characteristics have been reported in connection with VCFS, none present in 100 % of cases. Several complex of symptoms give rise to clinical suspicion; in particular, in small children, the association of palatoschisis with conotruncal cardiac defects.

The diagnostic hypothesis becomes stronger if other malformations are associated among facial asymmetry, hypocalcaemia, equinus foot, laryngomalacia, inguinal or umbilical hernias, and hypospadia. Febrile convulsions, epileptic seizures, and tetany (due to hypocalcaemia) can be early manifestations of the syndrome. Stroke or cortical atrophy is also common.

Lower limb pain and nocturnal leg cramps further characterize VCFS. Tethered cord has been found in some patient. Foot equinus-varus deformity is present in 10 % of cases.

Mental delay is present only in a minority of patients, and IQ is generally borderline or slightly below average. Children initially present psychomotor retardation, but have a good recovery around the age of 4 years. Language delay is in part attributable to phonation and articulation problems caused by the malformations.

Psychiatric disorders, heralded by prodromes in childhood, are evident in adults with

attention deficit and hyperactivity, obsessive-compulsive disorder, dysthymia, and cyclothymia. Around 20 % of VCFS become psychotic in adulthood [17].

17.7.4.3 Diagnostic Markers

Genetic – Chr 22q 11.2 microdeletion.
Brain MR – Structural abnormalities in the temporal and temporomesial regions.

17.7.4.4 Prognosis

Treatment is supportive. As usual, quality and life expectancies (nearly normal) depend on the amount of intellectual impairment. The large majority of children with VCFS have successful corrections of heart diseases and will have normal life spans. The risk for severe psychiatric illness is 25 times higher than in the general population.

17.7.5 Down Syndrome (DS)

Key Facts

- **Terminology and definitions** – Down syndrome (alias Trisomy 21) is an ID caused by the presence of a third copy of chromosome 21.
- **Clinical features** – Incidence: 1/1000 births. Maternal age increases the risk of having a Down child. Symptoms: small head with a flat looking face, congenital heart defects, hearing loss, ophthalmic disorders, endocrine deficiencies, and impaired mental and social status.
- **Diagnostic markers.**
  - **Genetics** – Trisomy 21.
- **Top differential diagnoses** Others IDs.
- **Prognosis.**
  - **Principles of treatment** – Supportive.
  - **Disability** – Survival 91 % at one and 85 % at 10 years of age.
    Survival 88.9 % until 15 years, and 87.5 % until 25 years. Many adults live into their late sixties and seventies.

17.7.5.1 Definition

Down syndrome (DS) (alias Trisomy 21) is an ID caused by the presence of a third copy of chromosome 21.

17.7.5.2 Clinical Features

With an incidence of 1/1000 births, DS is the most common chromosomal abnormality in children. Maternal age increases the risk of having a Down child. At age 40 the chance is one in 84, 1/44 at age 50 [18]. The older age of the father generates a higher risk of having an affected child in women older than 35 years but not in younger women.

DS phenotype includes a number of distinguishing features:

(a) Abnormally shaped and small head with a flat looking face, flattened nose, small ears and mouth, and upward slanting small eyes with epicanthal folds at the inner corners.
(b) Congenital heart defects, hearing loss, ophthalmic disorders, endocrine deficiencies, orthopedic problems, skin and dental abnormalities, obesity, seizure disorders, leukemia, early mortality, and Alzheimer's disease (AD).
(c) Impaired mental and social status, expressive language and verbal working memory deficits, and short attention span and slow learning.

Most individuals with Down syndrome have mild or moderate intellectual disability with some cases having severe deficits.

Atrioventricular septal defect is the most common congenital heart disease reported in DS, with a mortality rate 5–7 times higher than in normal population.

17.7.5.3 Prognosis

The survival rate in DS has improved with time reaching up to 91 % and 85 % at 1 and 10 years of age, respectively. Corrective surgery for congenital cardiac problems, the major cause of mortality in infants with DS, has played a significant role in the substantial decrease in mortality and has changed the demographic composition of people with DS. Survival until 15 and 25 years was 88.9 % and 87.5 %, respectively, in a New York State study, and many adults with DS are now living into their late sixties and seventies [19].

Children with Down syndrome (DS) have an increased risk to develop acute myeloid leukemia, and adult DS are more likely to develop younger onset alzheimer. Expectancy of life of DS is similar to that of the reference group until 30 years of age. The cause of mortality higher than in a control population after age 30 has been attributed to premature or accelerated aging and to development of AD. Nevertheless, 30–40 % of DS never show any, or only mild, signs of dementia.

As a whole, with proper health care, the mean life expectancy of DS is around 50–60 years in the developed world [20].

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Toxic and Deficiency Encephalopathies

18

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Abbreviations

CT, computed tomography; EEG, electroencephalography; ETKA, erythrocyte transketolase activity; HE, hepatic encephalopathy; ICU, intensive care unit; KS, Korsakoff's syndrome; MRI, magnetic resonance imaging; TDE, Toxic and deficiency encephalopathies; WE, Wernicke's encephalopathy

Key Facts

- **Definition** – TDE are a group of neurological disorders characterized by an altered mental status in the absence of primary structural brain disease.
- **Clinical features** – Altered level of consciousness and activity, global changes in cognition, a fluctuating course with disturbances in the sleep-wake cycle, and asterixis and myoclonus.
- **Diagnostic markers**
  - **Blood** – Search for metabolic and infectious derangements and toxicologic screening
  - **CSF** – Mandatory when the cause of confusional state/delirium is not obvious; indicated if fever is present
  - **CT/MRI** – Can show a widespread, symmetric pattern of injury of the deep gray nuclei and cerebral cortex
  - **EEG** – To exclude seizures and to confirm global cerebral dysfunction. Triphasic waves present in hepatic, uremic, and septic encephalopathy. The degree of abnormalities usually correlates with the severity of TDE.
- **Top differential diagnoses** – Cerebrovascular disease, infections, nonconvulsive status epilepticus, traumatic brain injury, dementia, psychiatric disorders
- **Prognosis**
  - **Treatment** – Related to the underlying condition.
  - **Disability** – TDEs usually are reversible events. Risk factors for incomplete recovery are duration of encephalopathy and its severity, advanced age, and preexisting neurodegenerative disease.

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18.1 Terminology and Definitions

Toxic and deficiency encephalopathies (TDE) are a group of neurological disorders characterized by an altered mental status in the absence of primary structural brain disease. Typically, they are caused by the failure of organs other than the nervous system, the presence of endogenous or exogenous toxins and drugs, or the deficiency of a nutritional substrate [1]. The causes of TDE are various (Table 18.1) and most cases are reversible, making important prompt recognition and treatment. However, certain forms, for instance Wernicke's encephalopathy, may result in permanent structural damage if untreated.

18.2 Clinical Features

The commonest clinical features of TDE are nonspecific and do not reliably identify a particular etiology; they include [1]: (1) mental status abnormalities; (2) motor system abnormalities; (3) seizures; (4) cranial nerve abnormalities

1. Mental status abnormalities are always present and range from subtle abnormalities to confusional state, delirium, stupor, or coma [2].
2. Motor system abnormalities include: tremor, asterixis, multifocal myoclonus, paratonia, alterations of deep reflexes, and Babinski.
3. Seizures: usually generalized tonic-clonic; sometimes focal, multifocal, and partial complex.
4. Cranial nerve abnormalities. The pupillary light reflex and vestibular responses are almost always present in patients with TDE, even in patients in deep coma, but can be blunted. In cases with more severe encephalopathy, dysconjugate roving eyes movement may occur [2].

Table 18.1 Common causes of toxic-deficiency encephalopathies

Systemic organ failure
Liver failure: acute, chronic
Renal failure: acute, chronic
Cardiac failure
Pulmonary disease: hypoxemia and hypercarbia/hypercapnia
Nutritional deficiency
Vitamin B_1 deficiency (Wernicke's encephalopathy, Korsakoff's syndrome, Marchiafava-Bignami disease)
Vitamin B_{12} deficiency
Folate deficiency
Niacin deficiency
Drugs and toxins
Drugs of abuse (e.g., ethanol, heroin, hallucinogens)
Prescription medications (e.g., opioids, sedative-hypnotics, antipsychotics, skeletal muscle relaxers)
Withdrawal states (e.g., ethanol, benzodiazepines)
Inhaled toxins (carbon monoxide, cyanide, hydrogen sulfide)
Infections
Sepsis
Systemic infections
Fever-related delirium

18.3 Diagnostic Markers

Detailed analysis of clinical history and use of medications are imperative.

A complete laboratory screening is necessary [3].

- *Blood gas determination*: In hyperventilating patients respiratory alkalosis is most commonly due to early sepsis, hepatic failure, early salicylate intoxication. Metabolic acidosis usually reflects uremia, diabetic ketoacidosis, lactic acidosis, methanol and ethylene glycol intoxication, late phases of sepsis
- *Urine, blood, and cerebrospinal fluid* (CSF) culture are indicated if fever is present
- *Toxicological screening* should be performed for suspected intoxications
- CSF – Mandatory when the cause of confusional state/delirium is not obvious
  - *EEG* – To exclude seizures and to confirm global cerebral dysfunction. Triphasic waves are detectable in hepatic, uremic, and septic encephalopathy. The degree of abnormalities usually correlates with the severity of TDE [4].

– TC/MRI – Can show a widespread, symmetric pattern of injury of the deep gray nuclei and cerebral cortex.

18.4 Top Differential Diagnosis

Cerebrovascular disease, central nervous system infection, nonconvulsive status epilepticus, traumatic brain injury, dementia, psychiatric disorders.

18.5 Prognosis

18.5.1 Principles of Treatment

The treatment of TDE is related to the underlying condition (see below specific etiology). However, regardless of the cause, some general measures should be considered, in particular [3]: discontinuation, if possible, of all drugs with potential toxicity to the central nervous system and avoidance of physical restraints. Restraint in a medical inpatient unit is associated with a threefold increased odds of persistent delirium.

Haloperidol: To treat severe agitation except in cases of alcohol withdrawal, anticolinergic toxicity, and benzodiazepine withdrawal.

Thiamine: For patients with a history of alcoholism, malnutrition, renal failure on hemodialysis, cancer.

18.5.2 Disability

TDE is common among patients admitted to intensive care units (ICU); older patients and those with underlying dementia are at greatest risk. Other possible risk factors for TDE include nutritional deficiency, infection, temperature dysregulation, and failure of multiple organ systems. The presence of delirium is an independent risk factor for mortality and prolonged hospitalization in patients receiving mechanical ventilation [5]. TDE is generally considered a reversible condition. However, severe TDE, particularly if causing coma, is a marker for significant morbidity and mortality. Underlying etiology, severity, and duration of coma were found to be independently associated with outcome in a series of 500 patients with medical causes of coma [6–8]. Hypoxic-ischemic coma was associated with a 58 % mortality (see Chap. 5) and a 31 % incidence of persistent vegetative state or severe disability, while other metabolic causes were associated with 47 % mortality and 21 % incidence of persistent vegetative state. Clinical signs predictive of these poor outcomes [7] included: (1) absent corneal or pupillary response at 24 h, (2) motor response poorer than withdrawal at 3 days, and (3) absent roving eye movements at 7 days.

Patients with so-called good outcomes may not be unaffected. Persistent neurological and psychiatric disturbances are reported in up to 32 % of patients with TDE after discharge from ICU [9]. Cognitive impairment is usually diffuse but more prominent in the areas of verbal fluency, working and visual memory, psycho-motor speed, and visual construction abilities. Depression is common, affecting 36 % of patients. Duration of delirium during the acute phase of hospitalization is longer among patients who develop neuropsychological impairment. Advanced age, low premorbid intelligence, hypoxia, cerebrovascular and peripheral vascular disease are also negative prognostic factors [10].

18.6 Hepatic Encephalopathy (HE)

18.6.1 Terminology and Definitions

HE is the result of hepatic insufficiency from acute liver failure or cirrhosis or from portosystemic shunting, even in the absence of intrinsic liver disease. Overt HE consists of neurological and psychiatric abnormalities that can be detected by bedside clinical tests, whereas minimal HE can only be distinguished by specific psychometric tests [11]

18.6.2 Clinical Features

Impaired mental status and impaired neuromotor function such as hyperreflexia, hypertonicity, and asterixis [11].

18.6.3 Diagnostic Markers

- *Blood* – Usually elevated arterial and venous ammonia, abnormal liver function and coagulation, decreased albumin, mild respiratory alkalosis, and hypoxemia
- CSF – Increased glutamine
- *CT* – To exclude other causes, diffuse cerebral edema in acute HE
- *MRI* – Bilateral T1WI hyperintensity in basal ganglia, particularly globus pallidus [12].
- *EEG* – (see above)
- *Psychometric tests* – Disturbances in attention, visuospatial abilities, fine motors kills, and memory [13].

18.6.4 Prognosis

18.6.4.1 Principles of Treatment

The management of acute HE should focus on providing supportive care, identifying and treating any precipitating causes, reducing blood ammonia concentration, and assessing the need for long-term therapy and liver transplant evaluation [14]

18.6.4.2 Disability

Approximately 70–80 % of patients with overt HE improve after identification and correction of precipitating factors. Rapid response to first-line medical therapy is usually observed within 24–48 h of initiation of treatment. Once patients show clinical improvement, then the prevention of recurrent HE becomes important, including reinforcement of compliance with treatment [15]. Patients with overt HE may have persistent and cumulative neurological deficits despite an apparent normalization of mental status after treatment. The number of episodes of overt HE correlates with the severity of residual impairment [16]. Fulminant hepatic failure is usually the result of massive necrosis of hepatocytes and is defined as a syndrome in which the sign of encephalopathy develops within 8 weeks from the onset of liver disease in a patient with a previously normal liver. In this condition, despite intensive treatment, patients who become comatose have an 80–85 % mortality [15].

18.7 Uremic Encephalopathy

18.7.1 Terminology and Definitions

Encephalopathy associated with acute or chronic renal failure.

18.7.2 Clinical Features

Lethargy, irritability, disorientation, hallucinations, rambling speech. Tremor, myoclonus, and asterixis are common, tetany may be present. Generalized, focal motor seizures or epilepsia partialis continua may occur. Coma may occur especially in acute renal failure [17].

18.7.3 Diagnostic Markers

- *Blood* – Abnormal renal tests
- *Neuroimaging* – May be required to exclude other diagnoses
- *EEG* – Prominence of slow waves (see above)

18.7.4 Prognosis

18.7.4.1 Principles of Treatment and Disability

Acute uremic encephalopathy reverses with dialysis, although a lag time of 1–2 days is usually required before mental status normalization. Subtle cognitive difficulties may persist. Phenytoin and phenobarbital are the mainstays in seizure treatment [17]. Two important neurological syndromes related to dialysis are recognized: dialysis-disequilibrium syndrome and dialysis-dementia syndrome [17]. Dialysis disequilibrium syndrome can occur during or immediately after treatment by either hemo or peritoneal dialysis and is usually characterized by headache, nausea, muscle cramps and twitching, delirium, and seizures. This entity is usually self-limiting and subsides over several hours to days. Slow dialysis and addition of osmotically active solute to the dialysate can prevent the condition. Dialysis-dementia syndrome is a subacute, progressive,

and often fatal disease that presents with dysarthria, dysphasia, apraxia, personality changes, myoclonus, seizure, and finally dementia. In most cases, it progresses to death in 6 months. Aluminum levels in the brains of patients with the syndrome are higher than in those of control groups. The aluminum content of dialysate fluid is the probable source of aluminum and the most likely cause of the syndrome. Chelation with deferoxamine is the treatment of choice [17].

18.8 Wernicke's Encephalopathy (WE)

18.8.1 Terminology and Definitions

WE is an acute encephalopathy due to thiamine deficiency. Although usually associated with chronic alcoholism, WE occurs also in the setting of poor nutritional state, increased metabolic requirement, or inadequate dietary intake [18]

18.8.2 Clinical Features

The classic triad of WE includes encephalopathy, oculomotor dysfunction, and gait ataxia. Other frequent findings include hypothermia and postural hypotension, reflecting involvement of hypothalamic and brainstem autonomic pathways [19].

18.8.3 Diagnostic Markers

WE is usually a clinical diagnosis. Laboratory and neuroimaging studies are helpful. However, there is no single test with sufficiently high diagnostic accuracy. The first imperative is to administer thiamine, rather than confirm the diagnosis, whenever WE is considered.

- *Blood* – Serum thiamine level and erythrocyte transketolase activity (ETKA) may be depressed, serum pyruvate may be increased
- *CSF* – Mild elevation in protein or normal
- *EEG* – About half of patients show diffuse slow activity
- *CT* – Often normal; or symmetric, hypodensity in the diencephalon, midbrain, and periventricular regions that may be enhanced
- *MRI* – Abnormalities on T2-weighted, FLAIR, and diffusion weighted images in the periacqueductal regions, medial thalami, and bilateral mammillary bodies. MRI abnormalities sometimes enhance but are typically reversed with prompt treatment. Shrunken mammillary bodies may be seen as a late residual finding [12].

18.8.4 Prognosis

18.8.4.1 Principles of Treatment

Suspected WE requires immediate parenteral administration of thiamine (500 mg i.v. over 30 min, three times daily for 2 consecutive days and 500 mg intravenously or intramuscularly once daily for an additional 5 days). Administration of glucose without thiamine can precipitate or worsen WE. Daily oral administration of 100 mg of thiamine should be continued until patients are no longer considered at risk [20].

18.8.4.2 Disability

Untreated WE is progressive and leads to coma and death. The mortality, even with thiamine treatment, is 10–20 % [18]. Prompt treatment improves ocular signs within hours to days, confusion subsides over days and weeks, gait disturbances resolve much more slowly, and in one third or more of cases, gait may be abnormal even months after treatment. In the largest reported series, residual deficits were the rule. While gaze palsies recovered completely in most cases, 60 % had permanent horizontal nystagmus. Only about 40 % recovered from ataxia, remaining deficits ranged from inability to walk to a wide-based slow gait. As the global confusional state receded, deficits in learning and memory become more obvious; the latter recovered completely in only about 20 % of cases, the remainder had a permanent amnestic syndrome (Korsakoff's syndrome) [18].

18.9 Korsakoff's Syndrome (KS)

18.9.1 Terminology and Definitions

Korsakoff's syndrome (KS) is a late neuropsychiatric manifestation of Wernicke encephalopathy (WE). KS is seen most frequently in alcohol abusers after an episode of WE, and most patients with KS show typical WE lesions. In contrast, KS is a less frequent sequelae of WE in non-alcohol abusers, suggesting that ethanol neurotoxicity is a contributing factor [18].

18.9.2 Clinical Features

KS is characterized by marked deficits in anterograde and retrograde memory with relative preservation of other cognitive skills. Confabulation is a feature in some but not all cases. Apathy is very common. Alertness, attention, and social behavior are relatively preserved and patients are unaware of their illness [18].

18.9.3 Prognosis

18.9.3.1 Principles of Treatment and Disability

Despite treatment with thiamine, patients with KS rarely recover. Improvement in memory functions is slow and usually incomplete and those who improve usually do so after a 1-month delay or longer. Many patients require at least some form of supervision and social support, either at home or in a chronic care facility. There are anecdotal reports of improvement in attention and memory with the use of acetylcholinesterase inhibitors and memantine but there is no controlled study [21, 22].

18.10 Marchiafava-Bignami Disease

18.10.1 Terminology and Definitions

Marchiafava-Bignami disease is a rare disorder characterized by demyelination or necrosis of the corpus callosum and adjacent subcortical white matter that occurs predominantly in malnourished alcoholics [23]. A few cases have been described in non-alcohol abusers, suggesting that alcohol alone is not responsible for the lesion.

18.10.2 Clinical Features

The clinical hallmarks of the disease are dementia, spasticity, dysarthria, and inability to walk.

18.10.3 Diagnostic Markers

- *CT* – Hypodense areas in portions of the corpus callosum. MRI: discrete or confluent areas of the corpus callosum with decreased T1 signal and increased T2 signal [23]. Alcohol abusers without liver disease, amnesia, or cognitive dysfunction show thinning of the corpus callosum on MRI and at autopsy, suggesting that alcohol or malnutrition damages the corpus callosum commonly in the absence of the necrotic lesions of Marchiafava-Bignami disease [24].

18.10.4 Prognosis

18.10.4.1 Principles of Treatment and Disability

Aggressive nutritional supplementation along with a reduction in drinking can prevent the development of Marchiafava-Bignami disease in alcohol abusers. The course of the disease may be acute, subacute, or chronic. Patients may lapse into coma and die, survive for many years in a demented condition, or occasionally recover. An interhemispheric disconnection syndrome has been reported in survivors [23].

18.11 Vitamin B_{12} Deficiency

18.11.1 Terminology and Definitions

Vitamin B12 or cobalamin deficiency may be responsible for different neurological manifestations including peripheral neuropathy, myelopathy, and encephalopathy.

18.11.2 Clinical Features

Paresthesias in the hands or feet are often present at onset. Weakness and unsteadiness of gait are the next most frequent complaints. Cerebral symptoms include mental slowing, depression, confusion, hallucinations, delusions. Some patients present only cognitive and psychiatric symptoms.

A myelopathy may develop with pyramidal tract dysfunction and sensory ataxia ("combined sclerosis" with degeneration of the posterior and lateral columns of the spinal cord), optic atrophy and centrocecal scotoma is sometimes present [25].

18.11.3 Diagnostic Markers

- *Blood* – Macrocytic anemia, low serum vitamin B12 or elevated metabolite (homocysteine, methylmalonic acid) levels may be present. Measurement of antibodies against parietal cell and intrinsic factor and Shilling's test should be considered to assess an underlying cause of malabsorption [25].
- *Neurophysiology* – Abnormal visual and somatosensory evoked potentials. *EEG* – Nonspecific abnormalities in cases with encephalopathy (see above).
- *MRI* – In encephalopathy is characterized by deep white matter lesions on T2-weighted images. *MRI* – In myelopathy may be characterized by abnormalities in the lateral and posterior columns of spinal cord [25].

18.11.4 Prognosis

18.11.4.1 Principles of Treatment and Disability

Patients with clinically overt vitamin B_{12} deficiency should be treated with parenteral vitamin therapy aimed at replenishing the total body pool. With adequate treatment, at least partial improvement can be expected. Most of the symptomatic improvement occurs during the first months of therapy, although it may not be complete for a year or more. The need for early diagnosis and treatment is underlined by the observation that remission correlates inversely with the time lapse between onset of symptoms and initiation of therapy. The myelopathy is least likely to make a complete recovery [25]. In a literature review of 57 cases of subacute combined degeneration, a complete recovery was reported only in 22 % of cases. Factors showing a strong association with complete resolution of signs and symptoms include absence of sensory level, Romberg and Babinski sign, and spinal cord atrophy. In addition, the male gender, absence of anemia, presence of Lhermitte's sign, and age <50 years were also strongly associated with complete resolution of signs and symptoms [26].

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Inborn Errors of Metabolism

19

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Abbreviations

AAs, amino acids; ACEi, angiotensin converting enzyme inhibitors; AD, autosomal dominant; AEDs, antiepileptic drugs; ALF, acute liver failure; AR, autosomal recessive; ARBs, angiotensin receptor blockers; ASL, argininosuccinic acid lyase; ASS1, argininosuccinic acid synthetase; ATP7A, ATPase7A; ATP7B, ATPase7B; BH_4, tetrahydrobiopterin; C5DC, glutarylcarnitine; CBS, cystathionine beta synthase; CDCA, chenodeoxycholic acid; CPS1, carbamoylphosphate synthetase 1; CSF, cerebrospinal fluid; CT, computed tomography; CTX, cerebrotendinous xanthomatosis; DHPR, dihydropteridin reductase; DRPLA, dentatorubropallidoluysian atrophy; DWI, diffusion weighted imaging; EEG, electroencephalogram; ERG, electroretinography; ERT, enzyme replacement therapy; FD, Fabry disease; FDG, fluorodeoxyglucose; GA-1, glutaric aciduria type 1; GC/MS, gas chromatography/mass spectrometry; GCDH, glutaryl-CoA-dehydrogenase; GL-3 or Gb3, globotriaosylceramide; GTPCH1, guanosine triphosphate cyclohydrolase 1; HDL, high density lipoprotein; HMG-CoA, hydroxymethylglutaryl coenzyme A; IEMs, inborn errors of metabolism; IVA, isovaleric aciduria; DRD, DOPA responsive dystonia; LNAA, large neutral amino acids; Lp(a), lipoprotein a; LVM, left ventricular mass; Lyso-SPM, lysosphingomyelin; MCAD, medium chain acyl CoA dehydrogenase; MD, Menkes disease; MHPA, maternal hyperphenylalaninemia; MMA, methylmalonic aciduria; MNGIE, mitochondrial neurogastrointestinal encephalopathy; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MSUD, maple syrup urine disease; MTHFR, methylenetetrahydrofolate reductase; NAA, N-acetylaspartic acid; NAGS, N-acetylglutammate synthase; NBIA, Neurodegeneration with brain iron accumulation; NCLs, neuronal ceroid lipofuscinoses; NPC, Niemann-Pick type C; OAs, organic acidurias/acidemias; OHS, occipital horn syndrome; ORNT1, ornithine/citrulline antiporter; OTC, ornithine transcarbamylase; PA, propionic aciduria; PAH, phenylalanine

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hydroxylase; PET, positron emission tomography; Phe, phenylalanine; PKU, phenylketonuria; PTPS, 6-pyruvoyltetrahydropterin synthase; S1P, shingosine-1-phosphate; SEP, somatosensory evoked potentials; SPECT, single photon emission computed tomography; TH, tyrosine hydroxylase; TIAs, transitory ischemic attacks; Tyr, tyrosine; UCDs, urea cycle disorders; UDCA, ursodeoxycholic acid; VSGP, vertical supranuclear gaze palsy; WD, Wilson's disease; WMI, white matter involvement; α-Gal A, α-galactosidase A

19.1 Introduction

The extensive term of inborn errors of metabolism (IEMs) [1] refers to inherited disorders in which a compromised step along a metabolic pathway leads to either the accumulation of toxic compounds, or to deficiency in energy production or utilization, or to a defect in the synthesis and the catabolism of complex molecules [2]. Needless to say, IEMs include a large and growing spectrum of disorders that differ from one another both from a pathogenetic point of view and in terms of disease expression, clinical course, outcomes, and prognosis [3].

This chapter is intended to give a brief clinical description and to illustrate outcomes and prognosis of several inherited metabolic diseases. The aim is to depict some IEMs, which generally arise in the pediatric age but frequently progress into adulthood [4–8]. In fact, most IEMs usually begin neonatally or early in infancy and present a severe clinical course with poor prognosis. Despite this, an increasing number of IEMs presents an atypical, slowly progressive,or late-onset course so that a pediatric illness is now becoming an adult neurologist concern.

Most of these disorders exibit wide and variable phenotypes. Furthermore, due to their rarity and the high mortality of patients in the pediatric age, there are few epidemiological data that can help to detail the courses of the diseases. In many cases, the prognosis is linked to a prompt diagnosis and treatment availability which are not achieved equally in all countries, thus changing worldwide prognostic data. In order to overcome these limits, we focused on those disorders that clinically begin in adulthood or on those with pediatric-onset but with a chronic progression until adulthood. The prognosis of the diseases will be referred as to the age groups (neonatal, infancy, childhood, youth and adolescence, and adulthood), unless prognostic data are clearly deduced from literature.

19.2 Disorders with an Acute Metabolic Decompensation

In this cluster of disorders, a metabolic decompensation represents the clinical overture or repeatedly reappears, from time to time, mostly during intercurrent illness (e.g., fever, infections), surgery and/or enhanced food intake. Therefore, prognosis and survival are strictly related to a prompt and subsequent dietary/pharmacological intervention to treat and prevent metabolic derangement with a likely better outcome if given during the first days of life. Conversely, a delayed diagnosis and repeated decompensating episodes throughout life can greatly impair the clinical outcome, worsening the impact of each specific disease.

19.2.1 Urea Cycle Disorders

Key Facts

- **Definition** – Urea cycle disorders (UCDs) [9] comprise several IEMs which impair the Krebs-Henseleit urea cycle
- **Prevalence** – 1:8,000–1:40,000 births
- **Clinical features** – Neonatal: irritability, feeding refusal, vomiting, hyperammonemia, and lethargy followed, if untreated, by seizures, hypotonia, respiratory alkalosis, and coma.
- **Childhood** – failure to thrive, frequent vomiting leading, if untreated, to lethargy and coma. Movement disorders, spastic tetraplegia, seizures, psychomotor retardation, diarrhea, and hypoglycemia may be present.
- **Adulthood** – episodes of confusion, stroke-like episodes, neuropsychological and psychiatric impairment
- **Diagnostic markers**
  - **Laboratory** – Elevated serum ammonia; plasma and urinary AAs analysis and urinary orotic acid leads to specific diagnosis of the different forms
  - **MRI** – Brain edema; T2W image in the newborns: increased signal between lateral nuclei of the globi pallidi and the putamina at.
- **Top differential diagnosis** – Viral infections; liver shunts or side effects of drugs (valproate); organic acidurias
- **Principles of treatment** – Reduction of dietary proteins; arginine or citrulline replacement; scavengers for nitrogen excretion
- **Prognosis** – Survival rate ranges from over 80 % in patients overall to more than 90 % for patients ≥ 12 years of age

19.2.1.1 Definition

Urea cycle disorders (UCDs) [9] comprise several IEMs which impair the Krebs-Henseleit urea cycle, involved in the breakdown of protein and metabolism of other nitrogen-rich molecules. These disorders result from:

A. Defects or total absence of any of five urea cycle catalytic enzymes (for instance, 1 – carbamoylphosphate synthetase I [CPS1, OMIM 608307] deficiency, 2 – ornithine transcarbamylase [OTC, OMIM 300461] deficiency, 3 – argininosuccinic acid synthetase [ASS1, OMIM 603470] deficiency, 4 – argininosuccinic acid lyase [ASL, OMIM 608310] deficiency, and 5 – arginase [ARG, OMIM 608313] deficiency)

B. Defects of CPS1 cofactor producer (N-acetyl glutamate synthase [NAGS, OMIM 608300] deficiency)

C. Or deficiency of two transporters (ornithine/citrulline antiporter [ORNT1, OMIM 608361] deficiency, glutamate/aspartate antiporter [Citrin, OMIM 603859] deficiency)

The urea cycle is involved in endogenous production of ornithine, arginine, and citrulline, in the clearance of nitrogen produced by protein turnover and other nitrogenous compounds and, partially, in nitric oxide production pathways.

Prevalence – 1:8,000–1:40,000 births

19.2.1.2 Clinical Features

In typical UCDs, the clinical picture reflects both the position of the defective enzyme and the severity of the deficiency.

Severe deficiency or total absence of the enzyme, in fact, leads to ammonia accumulation during the first days of life or early in infancy. Neonates or infants develop an acute presentation causing failure to feed, vomiting, multiple organ dysfunction, encephalopathy, and seizure. If untreated, the disease progresses to lethargy, hypoventilation, and coma.

In milder forms of the disease, ammonia tends to accumulate mostly during intercurrent illness or stress (e.g., surgery, prolonged fasting, or catabolism), protein overload, or specific drug treatment. Hyperammonemia is less severe and, although the symptoms vary from one type to another, patients usually present with loss of appetite, vomiting, behavioral abnormalities, and lethargy.

Atypical or late-onset forms of UCDs have increasingly been reported. Chronic symptoms are represented by episodes of failure to thrive and vomiting, lethargy, stroke-like episodes, neuropsychological and psychiatric impairment, seizures, visual loss, movement disorders (chorea, spasticity, cerebral palsy).

Summarizing, UCDs should be considered in patients displaying personal or family history of hyperammonemic crisis, or acute encephalopathies and in patients with hepatic, gastrointestinal, and psychiatric symptoms of unknown origin diagnosis of the different forms. Symptoms can suggest a specific enzyme/transporter defect such as ASLD (tricorrexis nodosa); ARG1 and ORNT1 (childhood progressive spastic paraparesis without hyperammonemic crisis); or CPS1, OTC, and ASS (neurological symptoms in the postpartum); and late-onset OTC (specific neuropsychological phenotype, coma post-partum).

19.2.1.3 Diagnostic Markers

Blood/urine – Elevated serum ammonia. Plasma and urinary amino acid (AAs) analysis, and urinary orotic acid lead to the specific diagnosis of the different forms.

Molecular genetic testing is required to confirm the diagnosis, carrier detection, and prenatal diagnosis.

Brain magnetic resonance imaging (*MRI*) – Hyperammonemia causes brain edema. In the newborns, T2W imaging can show increased signal between lateral globi pallidi and putamina. Mild cerebral and cerebellar atrophy and bilateral infarct of posterior putamen and insular cortex can be observed.

Brain magnetic resonance spectroscopy (*MRS*) – Elevated choline/creatine ratios and abnormal peak at 3.8 ppm, most likely representing arginine deposition [10], may be observed.

Pathology – Neuropathological evaluation reveals an alteration of astrocyte morphology including cell swelling in acute hyperammonemia, and Alzheimer type II astrocytosis (chronic hyperammonemia) with ulegyria in the most severe cases.

19.2.1.4 Top Differential Diagnosis

Differential diagnosis concerns disorders that alter liver function leading to hyperammonemia, such as viral infections, liver shunts, medications side effects (valproate), and Reye's syndrome. Other IEMs can present hyperammonemia, such as organic acidurias, mitochondrial disorders, and fatty acid oxidation disorders.

19.2.1.5 Principles of Treatment

The major therapeutic strategies are: (1) reduction of natural protein to decrease ammonia production, (2) replacement of amino acids such as arginine or citrulline, and (3) utilization of scavengers for nitrogen excretion such as sodium

benzoate and sodium phenylbutyrate or phenylacetate, and (5) liver/hepatocyte transplantation.

19.2.1.6 Prognosis and Outcomes

Since their first description in 1932, UCDs have shown a marked change in terms of survival rate, prognosis, and clinical picture. While survival was initially poor, and most of the severely affected patients died in the neonatal period due to the effects of hyperammonemia, current survival rates range from over 80 % [11] in patients overall, with higher rates of more than 90 % in individuals 12 years of age or older. The main factors that determine outcome are not fully understood, but duration and severity of hyperammonemia are the most important. Survival decreases with rising ammonium levels: coma lasting more than 2–3-days and very high ammonia levels (higher than 1000 μmol/L) are associated with irreversible neurological defects. Ammonium level ≤500 μmol per liter is a positive prognostic index for survival in nearly all hyperammonemic crises. Mental impairment is present in the majority of children surviving neonatal episodes of hyperammonemic coma, with 79 % having one or more developmental disabilities at 12–74 months of age. Most patients present a clinical history characterized by recurrent metabolic decompensation (with over 1,000 individual hospitalizations, in the long term); the neurological impairment progressively emerges with developmental delay, mental retardation, movement disorders, and psychiatric and behavioral symptoms. Neurological impairment can be considered as the result of a sort of single, acute injury that implies repetitive damage ultimately leading to nearly chronic progressive course). This is even more true regarding late-onset and atypical forms as a whole, so that, getting through metabolic derangements, UCDs represent a sort of new model of metabolic encephalopathy even in adults [12].

19.2.2 Organic Acidurias/Acidemias: Isovaleric Aciduria, Methylmalonic Aciduria and Propionic Aciduria (IVA, MMA, PA) (Table 19.1)

Key Facts

- **Definition** – Organic acidurias/acidemias (OAs) are disorders involving intermediate metabolism of branched-chain amino acids or lysine
- **Prevalence** – 1:30,000 births
- **Clinical features** – Poor feeding, vomiting, abnormal muscle tone, seizures, lethargy, and coma
- **Diagnostic markers**
  - **Laboratory** – metabolic acidosis with high anion gap, hyperlactacidemia, hyperammonemia, and ketosis. Molecular genetic testing. Neonatal screening of acylcarnitines profile
- **MRI** – globi pallidi hyperintensities in MMA and PA; different degree of white matter involvement; optic neuropathy
- **Top differential diagnosis** – shock and sepsis, mitochondriopathies, and fatty acids oxidation defects
- **Principles of treatment** – restricted intake of amino acids precursors; avoidance of catabolic stress
- **Prognosis and outcomes** – mental retardation, and movement disorders severely affect daily life activities and independence

Table 19.1 Classic organic acidurias

Disease	OMIM	Protein/gene	Main clinical symptoms	MRI	Prognosis [OMIM]
Isovaleric aciduria	243500	Isovaleryl CoA dehydrogenase- IVD	Acute: feeding refusal or aversion to protein, lethargy evolving to coma (due to dehydration and severe ketoacidosis), vomiting Chronic: developmental delay, leukopenia and thrombocytopenia or pancytopenia, cerebellar hemorrhage	Cerebellar hemorrhage (rare)	In 50 % of cases acute, severe neonatal illness, often with rapid death; 50 % of cases are chronic with asymptomatic intervals
Methylmalonic aciduria	251000	Methylmalonyl CoA mutase-MUT (*mut0*, *mut-*, *cbLB*)	Acute: failure to thrive, vomiting, lethargy evolving to coma (due to dehydration and severe ketoacidosis), pancreatitis, metabolic stroke Chronic: developmental delay, dysmorphisms, skin rashes, cardiomyopathy, hepatomegaly, nephritis and renal failure, cardiac abnormalities, leukopenia and thrombocytopenia or pancytopenia, megaloblastic anemia, hypotonia, dystonia, seizures, spastic ataxia, mental retardation	Basal ganglia stroke-like episodes (metabolic stroke) mainly involving globi pallidi but also putamina and caudate nuclei, cortical atrophy, delayed myelination, optic nerves involvement	Neonatal-onset associated with increased mortality. High frequency of developmental delay, and severe handicap. Cobalamin nonresponsive patients with neonatal-onset carry poor outcome. More favourable outcomes have late-onset patients mainly if cobalamin-responsive or classified as mut(–)
	251100	*Methylmalonic aciduria* (*cobalamin deficiency*) *type A –MMAA*			Onset in infancy. Responsive to vitamin B12 therapy
	251110	*Cobalamin transferase-MMAB*			Neonatal-onset. A subset of patients respond to vitamin B12
Methylmalonic aciduria and homocystinuria	277400	*Methylmalonic aciduria and homocystinuria cblC type –MMACHC*			Early-onset associated with more severe course and early death. Adolescent, adult-onset has neuropsychiatric symptoms. Variable response
	277410	*Methylmalonic aciduria and homocystinuria cblD type –C2orf25*			Good response to B12
	277380	*Methylmalonic aciduria and homocystinuria cblF type –LMBRD1*			Onset in infancy respond to vitamin B12
	614857	*Methylmalonic aciduria and homocystinuria cblJ type –ABCD4*			Onset at birth
Propionic aciduria	606054	Propionyl CoA carboxylase-PCCA	Acute: failure to thrive, decreased appetite, vomiting, tachypnea/apnea, lethargy evolving to coma (due to dehydration and severe ketoacidosis), acute encephalopathy with cerebellar hemorrhage and ischemic stroke of basal ganglia Chronic: psychomotor retardation, cardiomyopathy, hepatomegaly, pancreatitis, pancytopenia, thrombocytopenia, anemia, osteoporosis, dermatitis acidemia, axial hypotonia, limb hypertonia, dystonia, seizures		Onset at birth
		Propionyl CoA carboxylase-PCCB			

19.2.2.1 Definition

The classical organic acidurias/acidemias (OAs) are disorders involving intermediate metabolism of branched-chain amino acids or lysine [13]. Depending on the enzymatic defect, three major OAs have been defined: isovaleric aciduria (IVA, OMIM 243500), methylmalonic aciduria (MMA, OMIM 251000, 251100, 251110, 277400, 277410, 277380, 614857, 607481, 607568), and propionic aciduria (PA, OMIM 606054). IVA is due to a defect in isovaleryl CoA dehydrogenase (IVD) enzyme, encoded by the IVD gene [14]. MMA is divided in isolated MMA, due to methylmalonyl CoA mutase (MCM or MUT) enzyme deficiency (divided in mut^0 and mut^- variants referring to total or partial enzyme deficiency), or combined MMA with homocystinuria due to several complementation groups. Finally, PA is determined by a defect in propionyl CoA carboxylase (PCC) enzyme, encoded by PCCA and PCCB genes.

19.2.2.2 Prevalence

Estimated 1:30,000 births

19.2.2.3 Clinical Features

Usually, affected individuals are normal at birth or during the first days of life. Clinical symptoms, often starting in the neonatal period, are characterized by signs of a toxic encephalopathy, such as poor feeding, vomiting, abnormal muscle tone, seizures, lethargy, and coma (due to hyperammonemia and acidosis), resembling a sepsis-like clinical picture.

Some OAs variants can present with dysmorphic features, developmental delay, and abnormal tone without acidosis (see MMA cblC type). Patients present a high risk of infections and pancreatitis; the clinical course is characterized by recurrent life-threatening episodes of hyperammonemia and acidosis. Some patients present a less severe or late-onset phenotype with intellectual impairment, movement disorders such as ataxia, focal neurological signs, Reye-like syndrome, and psychiatric symptoms. Dystonia, chorea, and other movement disorders represent the result of basal ganglia metabolic strokes that are quite typical in some OAs (as for MMA and PA). Clinical impairment (less severe in IVA rather than in other OAs) is widely variable and asymptomatic patients have been described.

19.2.2.4 Diagnostic Markers

Severe metabolic acidosis with high anion gap, hyperlactacidemia with hyperammonemia and ketosis are the leading biochemical markers.

Laboratory – Urinary organic acids analysis by gas chromatography/mass spectrometry (GC/MS) should be performed.

Molecular genetic testing, enzymatic assay in lymphocytes or cultured fibroblasts confirms the diagnosis. Neonatal screening of acylcarnitines profile allows early diagnosis and treatment.

Brain MRI – Ranges from basal ganglia abnormalities (mostly globi pallidi hyperintensities in MMA and PA) and a different degree of white matter involvement together with optic neuropathy.

19.2.2.5 Top Differential Diagnosis

Nongenetic disorders such as shock, sepsis, mitochondriopathies, fatty acids oxidation defects, biotinidase deficiency, and urea cycle defects.

19.2.2.6 Principles of Treatment

Treatment is, in part, similar in all OAs, though strategies may vary due to the position of the metabolic blockade. In principle, treatment aims to restrict the intake of amino acids precursors, supply co-factors (for instance, thiamine in maple syrup urine disease, hydroxycobalamin in MMA and biotin in PA) which are helpful in detoxification or to increase residual enzymatic activity. Dietary therapy must be carefully adapted in the long-term run. Any source of catabolic stress (like intercurrent illness, vomiting, diarrhea, etc.) may lead to acute decompensation that must be promptly treated by restriction of metabolic toxic compound precursors or by dialysis together with critical care support for acidosis and hyperammonemia. Liver (PA and MSUD) and combined liver and kidney (MMA) transplantation are increasingly adopted for disease treatment with good results.

19.2.2.7 Prognosis and Outcomes

The availability of newborn screening and the new treatment sources for OAs have certainly had a profound effect on survival rates of classic OAs patients and, probably, an impact on clinical outcomes.

However, while the effects of neonatal screening and subsequent prompt treatment have been very efficacious in terms of survival rate and short-term development, the results on protracted neurodevelopmental outcomes still appear to be poor [15, 16], with mental retardation and movement disorders (ranging from dystonic tetraparesis, dystonic storming, chorea, and ataxia) greatly affecting the clinical picture, daily life activities, and independence.

19.2.3 Cerebral Organic Acidurias/Acidemias: Glutaric aciduria Type 1 (GA-1)

Key Facts

- **Definition** – Glutaric aciduria type 1 (GA-1) is an AR disorder caused by a defect in lysine, hydroxylysine, and tryptophan metabolism
- **Prevalence** – 1:40,000 births
- **Clinical features** – Macrocephaly and mild hypotonia at birth. Acute-onset deficits (often due to subdural hematoma), dystonia, spastic diplegia, and seizures often triggered by intercurrent illnesses
- **Diagnostic markers**
  - **Laboratory** – Newborn urinary screening for acylcarnitines shows elevated glutarylcarnitine (tandem mass spectrometry). Molecular genetic testing
  - **MRI** – Macrocephaly may be seen in asymptomatic patients. Dilated sylvian fissures with open opercula (bat-wing appearance), widened CSF spaces, frontotemporal atrophy, subdural hematomas, in symptomatic patients.
- **Top differential diagnosis** – Shaken baby syndrome
- **Principles of treatment** – Restriction in protein intake; lysine-free and low tryptophan diet; carnitine and riboflavin intake recommended
- **Prognosis and outcomes** – Most symptomatic patients carry severe handicaps, and 20 % die within 5 years of age

19.2.3.1 Definition

Glutaric aciduria type 1 (GA-1, OMIM 231670) is an autosomal recessive disorder caused by a defect in lysine, hydroxylysine, and tryptophan metabolism [17] with secondary glutaric acid, 3-hydroxyglutaric acid, and glutaconic acid accumulation. It is due to a defect in glutaryl-CoA-dehydrogenase (GCDH, OMIM 608801), a mitochondrial enzyme which converts glutaryl CoA.

19.2.3.2 Prevalence

1:40,000 births

19.2.3.3 Clinical Features

Patients are asymptomatic at birth or present with macrocephaly and mild hypotonia. Later, they present an acute clinical and neurological picture (typically with subdural hematoma [18]), which is generally triggered by intercurrent illnesses (e.g., acute infections, fever, dehydration, and vomiting), characterized by hypotonia, acute dystonia, spastic diplegia, and seizures. During the episodes, patients can also display feeding difficulties, hypoglycemia, hepatomegaly, and acidosis. This neurological picture is the result of an acute decompensation that can lead to coma and to brain injury mainly involving basal ganglia (striatal degeneration).

A minority of patients remains asymptomatic and do not experience acute decompensations.

19.2.3.4 Diagnostic Markers

Laboratory – Newborn screening by tandem mass spectrometry for acylcarnitines (elevated glutarylcarnitine [C5DC]) and gas chromatography/mass spectrometry for urinary organic acids (elevated glutaric, hydroxyglutaric, and glutaconic acids).

Molecular genetic testing should be performed to confirm the diagnosis.

Brain MRI – Macrocephaly may be observed even in asymptomatic and presymptomatic patients. On the contrary, dilated sylvian fissures with open opercula (bat-wing appearance), widened CSF spaces, and frontotemporal atrophy have been reported in symptomatic patients. Delayed myelination, subdural hematomas [19], and bilateral striatal hyperintensities [20] may also be present. DWI hyperintensity of the white matter, with a characteristic strip-like involvement of the corpus callosum, has been reported [21].

19.2.3.5 Top Differential Diagnosis

Differential diagnosis in patients with positive newborn screening includes medium-chain acyl CoA dehydrogenase (MCAD) deficiency and glutaric aciduria type 2 or maternal glutaric aciduria and renal insufficiency. Due to retinal hemorrhages, commonly present at clinical onset, and to subdural hematomas [19], easily detected by CT scan, shaken baby syndrome may be suspected. The neurological picture looks like athetoid/dystonic cerebral palsy.

19.2.3.6 Principles of Treatment

A restriction in protein intake, together with lysine-free and low tryptophan diet, and carnitine implementation is basic in a chronic patient's management. The diet must be frequently adapted since intercurrent diseases worsen the course of GA-1. Carnitine and riboflavin assumption is recommended.

Symptomatic drug therapy is based on antiepileptic (AEDs) and anti-dystonic drugs [17, 22].

19.2.3.7 Prognosis and Outcomes

Before newborn screening, glutaric aciduria caused a high mortality rate and poor outcomes with few patients remaining asymptomatic. Symptomatic patients carry a prognosis marked by irreversible neurological damage, and 20 % die within 5 years of age. In countries where newborn screening is available, neonatal diagnosis and treatment prevent acute derangements and severe brain injuries [23, 24].

19.3 Disorders Without Acute Metabolic Decompensation

In this cluster of disorders, patients do not experience acute metabolic life-threatening decompensation, but present a progressive and chronic picture.

19.3.1 Disorders of Amino Acid Metabolism

19.3.1.1 Phenylketonuria (PKU), Non-PKU Hyperphenylalaninemia

Key Facts

- **Definition** – PKU is an AR spectrum of disorders due to a defect of the phenylalanine hydroxylating system.
- **Prevalence** – 1:10,000 births in Europe.
- **Clinical features** – Untreated patients show decreased skin, hair, and iris pigmentation; musty body odor and eczema, microcephaly; delayed psychomotor development/mental retardation. Well-treated patients with good biochemical control are nearly asymptomatic.
- **Diagnostic markers** – Newborn screening for hyperphenylalaninemia; molecular analysis.
  - **MRI** – White matter involvement and volumetric alterations in basal ganglia.
- **Top differential diagnosis** – Defects in BH_4 metabolism.
- **Principles of treatment** – Restriction in Phe intake; BH_4, neutral amino acids supplementation, enzyme replacement therapy.
- **Prognosis and outcomes** – Excellent prognosis in patients diagnosed by neonatal screening or with mild variants. In early treated PKU adult patients, there may be impairment of selective, sustained attention, and working memory.

Definition

Phenylketonuria (PKU, OMIM 261600), the most frequent IEM, represents an autosomal recessive spectrum of disorders [25, 26] due to a defect of the phenylalanine hydroxylating system. This spectrum includes classic and mild PKU, due to phenylalanine hydroxylase (PAH) enzyme deficiency, and several forms of hyperphenylalaninemia due to the deficiency of tetrahydrobiopterin (BH_4), a critical PAH co-factor. PAH, in fact, converts phenylalanine (Phe) into tyrosine (Tyr) and requires tetrahydrobiopterin (BH_4) for its activity. The enzyme dysfunction, due to PAH gene mutations, results in intolerance of dietary protein intake with a build up of phenylketones which are toxic for brain development. High brain phenylalanine levels also undermine neurotransmitters biosynthesis, due to the competition with large neutral amino acids uptake through the blood–brain barrier. Besides classic PKU, hyperphenylalaninemia can also be determined by defects in the tetrahydrobiopterin (BH_4) regeneration pathway, which encompasses non-PKU BH_4 responsive hyperphenylalaninemias and other BH_4 metabolism-related disorders (including guanidine triphosphate cyclohydrolase 1 [GTPCH1], 6-pyruvoyltetrahydropterin synthase [PTPS], and dihydropteridin reductase [DHPR] deficiency), which will not be discussed in this chapter. Only GTPCH1 deficiency will be further described due to its clinical peculiarity and responsiveness to treatment.

Prevalence

1:10,000 births in Europe

Clinical Features

In classical PKU, the clinical picture is greatly related to the severity of enzyme deficiency and Phe levels.

Untreated patients show decreased skin, hair, and iris pigmentation (due to tyrosinase inhibition effect); musty body odor and eczema (due to high phenylalanine and phenylalanine metabolites excretion); secondary microcephaly; delayed psychomotor development/mental retardation; epilepsy; movement disorders and para/hemiparesis; behavioral and psychiatric disorders.

Treated patients with persistent hyperphenylalaninemia or with treatment poor compliance develop: suboptimal cognitive outcome; tremor, increased muscle tone; psychiatric problems; osteopenia and low bone mineral density; vitamin B_{12} deficiency.

PKU patients that strictly follow dietary treatment suggestions and present a good biochemical control and patients with milder forms of the disease display a nearly asymptomatic clinical course. These patients show no or subtle neurological and psychological symptoms mostly represented by brisk tendon reflexes, tremor, hyperhidrosis, school difficulties, anxiety, and phobias.

These clinical findings are also reported in adult PKU patients.

Diagnostic Markers

PKU is usually diagnosed by newborn screening and confirmed by plasma amino acid analysis.

Molecular analysis for mutation classification is strongly recommended. According to the level of Phe and molecular mutation, PKU has been recently classified as follows: classic PKU, moderate/mild PKU, mild hyperphenylalaninemia, non-PKU-hyperphenylalaninemia.

Brain MRI – White matter involvement (WMI) has been largely reported in PKU patients together with volumetric alterations in basal ganglia, somehow related to dopamine pathway dysfunction [27, 28].

Top Differential Diagnosis

Hyperphenylalaninemia (HPA) can be due to defects in BH_4 metabolism, which represents almost 3–5% of HPA. To rule out a BH_4 defect, pterins analysis in urine or blood spots and DHPR enzyme activity in erythrocytes should be performed.

Principles of Treatment

A dietary restriction in Phe intake must be started at the diagnosis. BH_4 loading test should be performed in all patients to ascertain who can benefit from this therapy. In patients who respond to BH_4, the diet can be relaxed or discontinued [29]. At any age [30], the main goal is to achieve a Phe level <360 μmol/L. Dietary restriction must be adapted over the years and according with personal Phe

tolerance. Other therapeutic options include large neutral amino acids (LNAA) supplementation, enzyme replacement therapy (providing the administration of modified phenylalanine ammonia lyase, now in phase III study), and somatic gene therapy [31–33].

Prognosis and Outcomes

The prognosis is excellent in patients diagnosed by neonatal screening and treated continuously from birth.

The picture of adult PKU patients and their long-term outcome is still controversial. In early treated PKU adults, impairment of selective and sustained attention and working memory have been reported. Moreover, the role of the brain MRI in identifying white matter lesions is still debated although several recent studies showed a strict relation between high Phe levels and brain lesions [34].

Maternal Hyperphenylalaninemia

Maternal hyperphenylalaninemia (MHPA) [35] refers to the possible effect of a poor metabolic control of affected HPA females during pregnancy and its teratogenic role in the newborn. In fact, Phe is crucial in some critical embryogenetic steps, so that high Phe levels in pregnant women is linked with facial dysmorphisms, microcephaly, mental retardation, congenital heart defects, and growth failure in the newborn.

19.3.1.2 Guanosine Triphosphate Cyclohydrolase 1 (GTPCH1) Deficiency: Autosomal Dominant and Autosomal Recessive

Key Facts

- **Definition** – GTPCH1 deficiency comprise a continuum of AD or AR disorders of biogenic amines
- **Prevalence** – Unknown
- **Clinical features** – AD-GTPCH1: lower limb dystonia with diurnal fluctuation at onset; progression to generalized dystonia; clear and enduring response to L-DOPA. AR-GTPCH1: hyperphenylalaninemia, developmental delay, severe cognitive impairment, seizures, limb dystonia, trunk hypotonia followed by generalized dystonia
- **Diagnostic markers**
  - **Laboratory – Blood** – Hyperphenylalaninemia in AR variants
  - **CSF** – Biogenic amines alterations and reduction of neopterin and biopterin
  - Molecular genetic testing
  - **Imaging – CT and MRI** – Not significant
  - **[^{18}F]-FDG PET** – Hyperactivity in the dorsal midbrain, cerebellum, and supplementary motor area; hypoactivity in motor and lateral premotor cortex and in the basal ganglia
- **Top differential diagnosis** – DYT1 related dystonia; myoclonic dystonias
- **Principles of treatment** – L-DOPA. Typical AR-GTPCH1 deficiency with hyperphenylalaninemia need BH_4, L-DOPA, and 5-hydroxytryptophan supplementation
- **Prognosis and outcomes** – Variable response to treatment. Most patients with DRD obtain complete remission of symptoms

Definition

Guanosine triphosphate cyclohydrolase 1 deficiency (GTPCH1, OMIM 600225) comprise a continuum of autosomal dominant (AD) or autosomal recessive (AR) inherited disorders [36] of biogenic amines. GTPCH1, in fact, is the rate-limiting enzyme in BH_4 cofactor biosynthesis, which leads to a secondary impairment of neurotransmitter metabolism (both dopamine and serotonin) with or without hyperphenylalaninemias.

Prevalence

Unknown

Clinical Features

AD-GTPCH1 deficiency, otherwise known as Segawa's disease or DOPA-responsive dystonia

(DRD, DYT5a), is generally characterized by normal developmental milestones until the age of 1 to 12 years. Afterwards, patients present a clinical picture characterized by lower limb dystonia. Dystonia presents diurnal fluctuations and has a clear and enduring response to L-dihydroxyphenylalanine (L-DOPA) administration. Adult onset is characterized by parkinsonism, while limb dystonia is less preminent [37, 38].

In contrast, AR-GTPCH1 deficiency presents with hyperphenylalaninemia and a severe neurological impairment characterized by developmental delay, severe cognitive impairment, seizures, limb dystonia with trunk hypotonia followed by generalized dystonia.

An intermediate autosomal recessive phenotype has also been depicted [39] presenting developmental delay and limb dystonia (with trunk hypotonia) with DOPA responsiveness.

Diagnostic Markers

In cases of childhood dystonia of unknown etiology, the first approach is a therapeutic trial with L-DOPA. Affected patients present a substantial and sustained response to the therapy. From a biochemical point of view, GTPCH1 catalyses the first step of BH_4 biosynthesis and enzyme dysfunction is associated to cerebrospinal fluid (CSF) biogenic amines and pterins abnormalities, with both reduction of neopterin and biopterin, which is quite typical for the disease. Hyperphenylalaninemia, in autosomal recessive variants, is found through newborn screening. Enzymatic assays and molecular genetic analysis give further information, but the CSF biochemical pattern is crucial for the diagnosis.

Brain MRI is normal.

[^{18}F]-FDG PET in DRD are characterized by metabolic hyperactivity in the dorsal midbrain, cerebellum, and supplementary motor area, and hypoactivity in motor and lateral premotor cortex and in the basal ganglia [40].

Top Differential Diagnosis

The clinical picture can resemble other early-onset primary dystonias (such as DYT1-related dystonia), myoclonus dystonias (like sarcoglycanopathies and DYT15 dystonia), and cerebral palsy or spastic paraparesis. Also, tyrosine hydroxylase (TH) deficiency and sepiapterin reductase (SR) deficiency, two other enzymes involved in biogenic amines metabolism, can present some kind of clinical and biochemical overlap, but differential diagnosis can be quite easily ruled out. Finally, the late-onset variant frequently presents as early-onset parkinsonism without a previous history of child-onset dystonia, so that genetic parkinsonism (for instance, PARK2 variants) and other parkinsonian-like syndromes should be excluded.

Principles of Treatment

L-DOPA plus a decarboxylase inhibitor are the mainstay in the treatment of DRD, with some criticalities in recommended dosages, owing to low dose responsiveness in some patients together with severe dyskinesia side effects after higher dosage, mostly in AR-GTPCH1 intermediate deficient patients.

Typical AR-GTPCH1 deficiency with hyperphenylalaninemia needs BH_4 supplementation and neurotransmitter replacement therapy (L-DOPA and 5-hydroxytriptophan). Clinical impairment is more severe and treatment responsiveness is widely variable so that several dosage adjustments are required.

Prognosis and Outcomes

This spectrum of disorders presents a widely variable clinical impairment, ranging from a mild dystonic syndrome, highly responsive to L-DOPA treatment, to a severe neurological picture characterized by developmental delay/mental retardation, seizures, and severe dystonia with incomplete responsiveness to treatment. Even in milder forms of the disease, though the neurological picture partially links to the age of onset of symptoms (with late-onset symptomatic patients presenting a less severe phenotype), a variable responsiveness to treatment has been repeatedly underlined with a complete remission of symptoms, which is not achievable in all patients. As a whole, DRD still represents a prototype of a disease showing a

dramatic positive recovery from therapy, while other disorders included in this nosological continuum need further studies to define the long-term prognosis and outcome.

19.3.1.3 Homocystinuria

CBS Deficiency

Key Facts
• **Definition** – Classic homocystinuria is a complex autosomal recessive disorder of methionine metabolism due to cystathionine beta synthase deficiency • **Prevalence** – 1:100,000 births • **Clinical features** – Multisystemic involvement with developmental delay and mental retardation, ectopia lentis, glaucoma, optic atrophy, retinal detachment and cataract, bone abnormalities, strokes, seizures, psychiatric symptoms • **Diagnostic markers** – High level of methionine in plasma and increased homocysteine in plasma and urine. Enzymatic assay in cultured fibroblasts and molecular genetic tests – **MRI** – White matter abnormalities and strokes • **Top differential diagnosis** – Marfan syndrome and sulfite oxydase deficiency • **Principles of treatment** – High dose of pyridoxine for vitamin B_6 responders. Protein/methionine restricted diet and vitamins supplementation (betaine, folate, and vitamin B_{12}) for vitamin B_6 nonresponders • **Prognosis and outcomes** – Good example of a treatable disorder; the life expectancy of patients with homocystinuria is reduced only if the disorder is untreated

Definition

Classic homocystinuria is a complex autosomal recessive disorder of methionine metabolism due to cystathionine beta synthase deficiency (CBS, OMIM 236200). A variant is pyridoxine (B6 vitamin) responsive; a second variant is non-responsive to pyridoxine. Respondent patients generally present a milder clinical phenotype.

Prevalence

1:100,000 births

Clinical Features

The clinical picture is characterized by a multisystem involvement with eye, skeletal, vascular, and brain symptoms characterized by developmental delay/mental retardation, myopia and ectopia lentis, glaucoma, optic atrophy, retinal detachment and cataract, bone abnormalities, strokes, seizures, and psychiatric symptoms.

Patients present a variable clinical picture with late-onset variants showing a poorly symptomatic or acute symptomatic picture.

Diagnostic Markers

Amino acid analysis detects a high level of methionine in plasma and increased homocysteine in plasma and urine. Newborn screening is available with the assays of methionine and homocysteine levels. The diagnosis is then confirmed by molecular genetic testing.

Brain MRI

Lacunar and large artery stroke can be detected (artery-to-artery embolism and dissection have also been reported) [41]. Diffuse white matter abnormalities are uncommon findings [42].

Top Differential Diagnosis

Marfan syndrome and sulfite oxydase deficiency must be excluded. The lens dislocation in homocystinuria is usually downward, while in Marfan syndrome it is upward [43]. The biochemical picture, with increased concentrations of homocystine/homocysteine or methionine, requires the exclusion of methionine transmethylation defects, methylenetetrahydrofolate reductase (MTHFR) deficiency, and cobalamin defects and other causes of homocystinuria (comprising nutritional aberrations).

Principles of Treatment

Treatment is based on:

1. Vitamin B_6 responders – Patients showing reduction of 30% or more of homocysteine/homocystine or methionine under oral pyridoxine are treated with a high dose of pyridoxine.
2. Vitamin B_6 non-responders – Require a protein/methionine-restricted diet and vitamin supplementation including betaine, folate, and vitamin B_{12} to prevent thrombotic events [44]. Surgery is suggested for ectopia lentis and prophylaxis with anticoagulant is mandatory during pregnancy. Oral contraceptives should be avoided.

Prognosis and Outcomes

This is a good example of a treatable disorder. The life expectancy of patients with homocystinuria is reduced only if the disorder is untreated. Thromboembolism is the most common cause of death. A close biochemical and therapeutical follow-up is effective in preventing most of the symptoms with consequential good clinical prognosis and outcomes.

19.3.2 Lysosomal and Other Storage Diseases

Key Facts

- **Definition** – FD is a lysosomal storage disease due to an X-linked defect of α-galoctosidase A
- **Prevalence** – 1:3,000–117,000 births, genetic variants included
- **Clinical features** – Onset between 3 and 10 years with neuropathic and abdominal pain, diarrhea/constipation, angiokeratoma, corneal changes, retinal vessels tortuosity, tinnitus/hearing loss, proteinuria, kidney failure, cardiomyopathy, stroke, lymphoedema, facial dysmorphisms
- **Diagnostic markers** – Deficient α-galactosidase activity in leukocytes or plasma. Genetic testing is mandatory for female patients
- **MRI** – Pulvinar T1W hyperintensities, basilar artery dolichoectasia, chronic white matter hyperintensities
- **Top differential diagnosis** – Rheumatic diseases; small fibers peripheral neuropathies of different cause
- **Principles of treatment** – Agalsidase alfa and beta enzyme replacement therapy
- **Prognosis and outcomes** – Before renal dialysis and transplant availability, survival was 41 years in males; renal transplant has improved survival to 58 years in males and 75 years in females

19.3.2.1 Fabry Disease (FD)

Definition

Fabry disease (FD, OMIM 301500) is the second most common (after Gaucher disease) progressive glycosphingolipid lysosomal storage disease [45]. It is due to an X-linked defect of lysosomal α-galoctosidase A (α-Gal A, EC3.2.1.22, OMIM 300644), resulting in accumulation of globotriaosylceramide (Gb3 or GL-3) and related glycosphingolipids (galabiosylceramide) in lysosomes of endothelial, renal, cardiac, and nerve cells. GL-3 storage starts before birth in placental tissue and progresses to organ failure (mostly heart and kidney but also gastrointestinal and respiratory systems) with multisystemic and neurological involvement (both peripheral and central nervous system are affected) [46, 47]. Fabry disease affects not only hemizygous male patients but also heterozygous females with a wide phenotypic heterogeneity.

Prevalence

1:3,000 – 117,000 including all variants [45].

Clinical Features

This disorder exhibits a wide spectrum of clinical phenotypes ranging from "classical" severe phenotype in affected males up to a nearly asymptomatic presentation occasionally observed in a few heterozygous females. The first clinical signs usually present between the ages of 3 and 10 years (a few years later in girls) with peripheral somatic and autonomic nerves involvement and other signs/symptoms such as: neuropathic chronic pain or "acroparesthesias", which may exacerbate with severe, acute, episodic crisis "Fabry crises", abdominal pain, diarrhea or constipation, angiokeratoma, corneal changes "cornea verticillata", retinal vessels tortuosity, tinnitus and hearing loss, minor facial dysmorphisms.

Patients display a progressive course with multisystemic involvement, which leads adulthood to: renal impairment up to renal failure; cardiac involvement (arrhythmias and left ventricular hypertrophia); cerebrovascular involvement (acute and chronic lesions); osteopenia.

Signs and symptoms are usually fully manifest in affected males while heterozygous females present a high phenotypic heterogeneity. The female spectrum includes nearly asymptomatic patients up to classic severe phenotypes presenting neuropathic pain, plus all the aforementioned clinical findings.

In both sexes, atypical variants (the most known is the cardiac variant) have also been described.

Diagnostic Markers

Newborn screening for Fabry disease demonstrates reduced α-galactosidase activity in leukocytes or plasma (dried blood spot).

Genetic testing is mandatory for female patients, due to the X chromosome transmission.

Plasma globotriaosylsphingosine or lyso-GL-3 is a useful biomarker to discern classical Fabry patients from subjects without the disease [48]. Lyso-GL-3 might correlate with white matter lesions load [49].

Brain MRI/CT – Basilar artery dolichoectasia has frequently been reported. Bilateral T1W hyperintensity is a characteristic neuroradiological sign of FD, but it is not a pathognomonic sign. Sometimes calcium deposit can be recognized in the pulvinar by CT scan. Chronic white matter abnormalities (usually symmetric) have been reported, with an increasing load according to ageing. All kinds of cerebrovascular manifestations, including cerebral venous thrombosis, can be detected [47].

Top Differential Diagnosis

Rheumatic diseases (such as rheumatic arthritis and fever, systemic lupus erythematosus, Raynaud's phenomenon) and other small fiber peripheral neuropathies should be excluded. Mitochondrial neurogastrointestinal encephalopathy (MNGIE disease) mimics earlier aspects of Fabry disease. Later in the course of FD, multiple sclerosis, due to the white matter involvement, celiac disease, Fahr, and parathyroid disorders must be ruled out.

Principles of Treatment

Since 2001, enzyme replacement therapy (ERT) with agalsidase alpha and beta has been approved in Europe as the specific treatment of FD. Recently, modified enzyme replacement and the use of active site chaperones have been proposed in patients presenting residual enzymatic activity.

Supportive drug treatment (including ACE inhibitors, antithrombotic and anticoagulant drugs) together with preventive measures (e.g., avoidance of cold that can trigger painful crisis) are recommended. Carbamazepine, gabapentin, and pregabalin are useful for neuropathic pain [46]. Renal dialysis and transplant are utilized in end-stage renal failure.

Prognosis and Outcomes

The natural history of Fabry disease is characterized by a variable, but severe clinical impairment with a later great impact on life expectancy. Before renal dialysis and transplant availability, the average age of death was 41 years in males. Renal transplants have likely changed the natural course of the disease, leading to a median lifespan of 58 years in males and 75 years in females. According to the Fabry Registry data, cardiovas-

cular disease (usually arrhythmia) was the most common cause of death.

Several studies have focused on the effect of ERT both on survival rate and clinical symptoms. Both drugs have proved to be effective, at a different extent, in increasing kidney, heart, and skin GL-3 clearance. Improvement of glomerular filtration, cardiac function, and reduction of pain severity have been reported [45]. Few data are available on long-term treatment.

A recent 10-year study has documented the long-term efficacy of agalsidase beta in a cohort of 52 adults [50]. The most favorable outcome was observed in younger patients with smaller amount of kidney impairment.

19.3.2.2 Niemann-Pick Type C Disease (NPC)

Key Facts

- **Definition** – NPC is a lipid storage neurovisceral disease due to NPC1 (95% of patients) and NPC2 (4%) gene mutations.
- **Prevalence** – 1:150,000 in Western Europe.
- **Clinical features** – Widely variable according to the age of onset. Fetal hydrops or ascites and prolonged cholestatic icterus in neonates. Hepatosplenomegaly, delayed motor development, and mental regression in infants and children. VSGP, ataxia/dystonia, gelastic cataplexy, cognitive decline, and psychiatric symptoms in adolescents and adults.
- **Diagnostic markers**
  - **Blood** – Low HDL-cholesterol, mildly elevated chitotriosidase, and normal acid sphingomyelinase activity. Elevated plasma oxysterols.
  - **Fibroblasts** – Positive "filipin test".
  - Molecular genetic test
  - **MRI** – Cerebral and cerebellar atrophy and thinning of the corpus callosum in advanced forms.
- **Top differential diagnosis** – Gaucher disease, GM2 gangliosidosis.
- **Principles of treatment** – Miglustat has been authorized for the treatment of NPC.
- **Prognosis and outcomes** – Death in a few days in most of the infants with neonatal-onset severe variants. The severe neurologic infantile form leads to death in 3–5 years. Late-onset variants present severe motor, cognitive, and psychiatric impairment. Miglustat is effective in stabilizing the disease in over 60 % of cases. Late-onset variants present the best response to treatment.

Definition

Niemann-Pick type C (NPC, OMIM 257220, 607625) disease is a lipid storage, neurovisceral disease that can present in perinatal period as well as in adulthood. It is due to NPC1 (95% of patients) and NPC2 (4%) gene mutations, which result in altered trafficking of endocytosed cholesterol [51–53] with secondary alterations of glycosphingolipids and sphingomyelin.

Prevalence

Geographic variability, 1:150,000 in Western Europe

Clinical Features

Clinical presentation is widely variable and partially linked to the age of onset. NPC should be considered in:

- Neonates showing fetal hydrops or ascites and prolonged cholestatic icterus (which resolve in 2–4 months) and hepatosplenomegaly. In a few patients, a fatal form of acute dramatic cholestatic or respiratory insufficiency has been rarely described.
- Infants and children presenting hepatosplenomegaly, developmental delay or motor and mental regression and central hypotonia, school problems (writing and attention difficulties mimicking dyspraxia), spasticity, intention tremor, and, rarely, seizure.
- Juvenile showing vertical supranuclear gaze palsy (VSGP) followed by clumsiness in walking evolving into ataxia, dystonia, and spasticity with pseudobulbar signs (swallowing impairment, dysartria) and gelastic cataplexy, school problems, seizures.

- Adult patients present splenomegaly (in 10% of cases organomegaly is not detectable at this stage), VSGP, gelastic cataplexy (typically laughter-induced), ataxia with disarthria/dysphagia and dystonia, psychiatric symptoms [53].

Niemann-Pick type C is easily suspected in fully symptomatic patients; diagnosis may be difficult in late-onset patients with psychiatric presentations or cognitive decline.

Diagnostic Markers

The clinical picture should suggest the diagnosis [54], mainly referring to organ involvement and accurate ophthalmological, neurological, and neurophysiological [55] assessment.

Blood – Low HDL-cholesterol, mildly elevated chitotriosidase, and normal acid sphingomyelinase activity (in contrast with Niemann-Pick type A and B disease) have been reported. Recent studies have demonstrated elevated plasma oxysterols as a diagnostic biomarker for NPC1 and NPC2 patients [51, 54].

Molecular genetic testing should always be performed.

Bone marrow – The presence of foam cells and sea-blue histiocytes confirm the diagnosis.

Fibroblasts – Positive "filipin test" is diagnostic.

Brain MRI – Is usually normal in the first stages of the disease; in advanced forms, MRI shows cerebral and cerebellar atrophy (mostly involving cerebellar vermis), thinning of the corpus callosum, white matter involvement mimicking leukodystrophy or multiple sclerosis [56].

Top Differential Diagnosis

In neonates, idiopathic hepatitis and other causes of cholestasis should be ruled out. In children presenting the full clinical picture, Gaucher disease, GM2 gangliosidosis, mitochondrial disorders, Wilson disease and other causes of dystonia or ataxias must be considered. In adolescence and adults with neurological and psychiatric impairment, degenerative dementias, and parkinsonisms (Steele-Richardson-Olzewski) must be considered with late-onset lysosomal diseases and primary psychiatric syndromes [51].

Principles of Treatment

In 2009, miglustat, a reversible inhibitor of glycosphingolipid synthesis, was approved in Europe for the treatment of NPC because of its efficacy in stabilizing the disease [57].

Physical therapy and symptomatic drug treatment for dystonia, seizure, cataplexy, and sleep disorders are recommended.

Prognosis and Outcome

NPC is a progressive disorder which generally leads to death within a few days (in patients with neonatal onset) due to liver failure or pulmonary insufficiency.

The severe neurologic infantile form leads to death within 3–5 years.

Patients with late-onset variants can survive until 40 years of age with a few patients surviving until the age of 70 years. Briefly, atypical late-onset forms tend to present a less rapid course with higher survival rate, but manifest with progressive, severe neurological impairment characterized by motor deficits, seizures, and psychiatric disorders. Death occurs due to dysphagia and pulmonary infections.

Since the introduction of miglustat, several studies have focused on its efficacy [57]. Overall, miglustat has proven to be effective in stabilizing the disease course up to 69 % of cases followed-up for 12 or more months. The late-onset variants give the best response to treatment; usually the side effects are few and treatable.

19.3.2.3 Cerebrotendinous Xanthomatosis (CTX)

Key Facts

- **Definition** – CTX is an autosomal recessive inherited lipid storage disorder due to mutations in CYP27A1 gene
- **Prevalence** – 1.9:50,000–100,000 among Caucasians
- **Clinical features** – Infantile-onset: diarrhea, childhood cataract. Xanthomas, neurologic, and psychiatric impairment in adolescents and adults
- **Diagnostic markers**
  - **Blood** – High plasma cholestanol, with normal or low plasma cholesterol. Enzymatic assay and molecular genetic testing gives further diagnostic data
  - **MRI** – Diffuse cerebral and cerebellar atrophy; focal white matter hyperintensities, *MRS*: decreased NAA and increased lactate
- **Top differential diagnosis** – Sitosterolemia and familial hypercholesterolemia
- **Principles of treatment** – Bile acids, vitamin E supplementation
- **Prognosis and outcomes** – Lowered life expectancy. Patients can die in infancy; more commonly survive until the fourth and sixth decades with progressive disability beginning between the fourth and the fifth decades of life

Definition

Cerebrotendinous xanthomatosis (CTX, OMIM 213700) is an autosomal recessive inherited lipid storage disorder due to mutations in CYP27A1 gene, which encodes the mitochondrial sterol-27-hydroxylase enzyme [58]. CTX is caused by a defect of bile acids biosynthesis leading to accumulation of bile acids, precursors in several organs and in the central nervous system (CNS).

Prevalence

Still controversial, 1.9:100,000 in general population.

Clinical Features

The disease should be suspected in patients presenting infantile-onset diarrhea, childhood-onset cataract, adolescent or adult with xanthomas, and adult-onset neurologic and psychiatric impairment [59].

The neurological picture is characterized by mental retardation/dementia (present in half of the patient over 20 years), dystonia, myoclonus [60], spinal cord lesion, cerebellar ataxia and atypical parkinsonism, pseudobulbar deficits, and peripheral neuropathy. Psychiatric symptoms are frequent.

Diagnostic Markers

Laboratory – Diagnosis is based on the presence of high plasma cholestanol, with normal or low plasma cholesterol, low chenodeoxycholic acid production with impaired bile acids synthesis, and increased bile alcohols.

Lactate, cholestanol, and apolipoprotein B concentrations are increased in plasma, cerebrospinal fluid (CSF), and brain. *Multianalyte assays* are being developed for early diagnosis and screening [61].

Enzymatic assay and molecular genetic testing gives further diagnostic data.

CT and MRI – Neuroimaging shows diffuse cerebral and cerebellar atrophy with cerebral peduncles involvement, white matter hyperintensities and cerebellar focal lesions, mainly involving dentate nuclei.

MRS – Proton magnetic resonance spectroscopy displays decreased N-acetylaspartate (NAA) peak with increased lactate, suggesting mitochondrial dysfunction. Lipid peaks may be found in cerebellar hemisphere [62].

Top Differential Diagnosis

Sitosterolemia and familial hypercholesterolemia need to be excluded.

Principles of Treatment

Treatment is based on bile acids supplementation (chenodeoxycholic acid [CDCA], ursodeoxycholic acid [UDCA], cholic and taurocholic acids), which reduces cholestanol levels and lowers bile alcohols, together with hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). Vitamin E supplementation, low-density lipoprotein apheresis, and liver transplantation have provided controversial results. Symptomatic therapy for neurological [63] and psychiatric symptoms, as well as surgery for xanthomas, may be useful.

Prognosis and Outcomes

Illness often begins with intractable diarrhea. Presenile cataracts result in poor vision. Xanthomas can cause motor restriction and joint deformities. Vascular disorders such as premature atherosclerosis (especially in the carotid and coronary vessels) can lead to stroke and myocardial infarction. The neurologic manifestations of CTX range from treatable seizures to neurologic devastation. Prognosis and outcomes are strongly related to the severity of the clinical picture at the time of the diagnosis. CTX severity varies considerably, but life expectancy is often lowered. Twenty percent of patients die despite therapy [64, 65] due to poor or no responsiveness to treatment. Patients can die in infancy, but more commonly survive until the fourth and sixth decades, with progressive disability usually occurring from the fourth to the fifth decades of life. Myocardial infarction and progressive mental deterioration with pseudobulbar palsies are common causes of death.

19.3.2.4 Neuronal Ceroid Lipofuscinoses (NCLS) (Table 19.2)

Key Facts

- **Definition** – NCLs are a group of lysosomal storage diseases due to the accumulation of osmiophilic lipopigments in brain, eye, liver, skin, and reticuloendothelial system
- **Prevalence** – 1.5 to 9:1,000.000 births
- **Clinical features** – Juvenile and adult NCL variants present with cognitive decline, motor impairment, chorea, loss of vision, seizures
- **Diagnostic markers** – The diagnosis is mainly based on clinical picture
  - **EEG** – Posterior predominant spikes and polyspikes with photosensibility and progressive background abnormalities
  - **Electroretinography** – Early extinction
  - **VEPs** – Low amplitude/isoelectric pattern
  - **SEPs** – Giant potentials in some patients
  - **Skin biopsy** – Lipopigments, enzymatic testing, and molecular genetic analysis
  - **MRI** – Progressive diffuse cerebral and cerebellar atrophy, leukoencephalopathy, basal ganglia involvement
- **Top differential diagnosis** – Leukoencephalopathies/leukodystrophies, peroxysomal disorders, epileptic encephalopathies, Niemann-Pick and Lafora disease, NBIA and GM2 gangliosidosis
- **Principles of treatment** – Mainly symptomatic
- **Prognosis and outcomes** – Early-onset variant presents a high rate of death before 10 years of age. Adult variants often show a protracted course (even until sixth or seventh decade). Disability is globally severe with heavy motor and cognitive impairment and drug-resistant seizures

Definition

Neuronal ceroid lipofuscinoses (NCLs) [66, 67] are AD or AR lysosomal storage diseases characterized by the accumulation of osmiophilic lipopigments in brain, eye, liver, skin, and reticuloendothelial system. Thirteen genes have been identified as causing NCLs. Conventionally, the NCLs are clinically sorted according to the age of onset and to the order of appearance of symptoms or referring to the type of enzyme/protein defect (see Table 19.2) for all pathologic variants).

Table 19.2 Table CLN1

Disease	OMIM	Protein	Main clinical symptoms	Variant	Age of onset	Prognosis [OMIM]
CLN1 or Haltia Santavuori disease	256730	PPT1	Cognitive and motor decline, visual loss, seizure	Classic infantile, late infantile, juvenile, adult	6–24 months	Variable severity, correlates with age at onset
CLN2 or Janský-Bielschowsky	204500	TPP1	Seizure, cognitive and motor decline, visual loss	Classic late infantile, juvenile	2–4 years	Death at 10–15 years
CLN3 or Spielmeyer-Sjögren disease	204200	Battenin	Seizure, cognitive and motor decline, visual loss, neuropsychological impairment	Juvenile	4–10 years	Death at 20–40 years
CLN4 or Parry disease	162350	DNAJC5	Cerebellar syndrome, seizure, myoclonus, dementia/ parkinsonism	Early juvenile to adult	20–50 years	Rapidly progressive
CLN5 or Finnish variant (juvenile variant previously CLN9)	256731	CLN5	Cognitive and motor decline, visual loss, seizure	Late infantile, juvenile, adult	4–7 years	Death at 13–30 years
CLN6 or Lake Cavanaugh (early juvenile), Costa Rican-Indian (late infantile), Kufs disease type A (adult)	601780	CLN6	Cognitive and motor decline, visual loss, seizure	Late infantile, juvenile, adult	18 months–8 years	Death in the mid-twenties
CLN7 or Turkish variant	610951	MFSD8	Visual loss, ataxia, myoclonus, neurodevelopment regression, seizure	Late infantile, juvenile, adult	2–7 years	Rapidly progressive, patients often wheelchair-bound
CLN8 or Northern epilepsy	610003	CLN8	Motor decline, seizure, visual loss	Late infantile	3–7 years	Decrease in seizure frequency in middle age; slowly progressive
CLN10	610127	CTSD	Congenital: microcephaly, respiratory insufficiency, status epilepticus Other variants: motor regression, ataxia, visual disturbances	congenital classic, late infantile, adult	all ages	null mutations (in CTSD) carries more severe phenotype with death within days
CLN11	614706	GRN	Seizure, behavioral impairment	Adult	15–50 years	Rapidly progressive

CLN12 and Kufor-Rakeb syndrome (KRS)	606693	ATP13A2	CLN12: learning difficulties, limb stiffness, Parkinson-like disease, spasticity, pseudobulbar signs, chorea, slow eye movements, cognitive decline KRS: atypical Parkinson disease, supranuclear palsy, dementia, chorea, aggressive behavior, visual hallucination, oculogyric crisis	Juvenile	12–16 years	Rapidly progressive (6–24 months), favorable initial response to L-DOPA
Adult Kuf disease type B	615362	CTSF	Cognitive and motor decline, behavior abnormalities	Adult	20–30 years	Progressive
CLN14	611726	KCTD7	Progressive myoclonus epilepsy, retinal involvement, neurodevelopmental delay	Infantile	8–9 months	Progressive severe phenotype

Prevalence

Geographical variability, 1.5 to 9:1,000,000 births

Clinical Features

Juvenile and adult NCL variants present with progressive cognitive decline, motor impairment (motor regression, chorea, myoclonus, ataxia, spasticity), loss of vision, seizures.

The presenting symptoms and the age of onset may vary between different diseases. Juvenile myoclonus characterizes some variants (CLN4, 7, 14); Parkinson/dementia-like diseases (CLN4, 12) or behavior impairment typifies CLN12, 13.

Diagnostic Markers

The diagnosis of NCLs is mainly based on clinical grounds.

Electroencephalogram (EEG) displays multifocal/focal traces with posterior predominant spikes and polyspikes with photosensibility and progressive background abnormalities.

Electroretinography (ERG) showing early extinction can further sustain the clinical approach.

Visual evoked potentials show a low amplitude/isoelectric pattern; *somatosensory evoked potentials* (SEP), in some cases, show giant potentials.

Skin biopsy for lipopigments, enzymatic testing, and molecular genetic analysis are mandatory for the ultimate diagnosis.

Brain MRI displays progressive diffuse cerebral and cerebellar atrophy, leukoencephalopathy together with (or without) basal ganglia signal changes (Fig. 19.1).

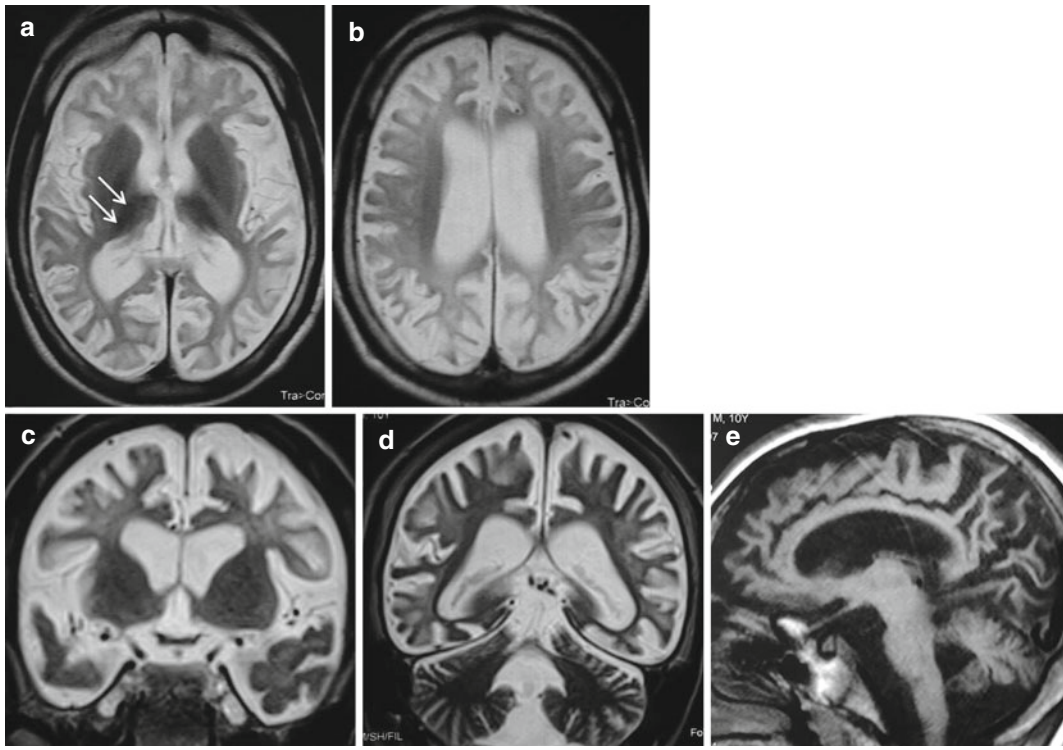

Fig. 19.1 NCL. Axial T2-weighted images, **a** and **b**, coronal T2-weighted images, **c** and **d**, and sagittal T1-wieghted image, **e**, demonstrate marked diffuse cerebral atrophy with sulci and ventricular enlargement and thinning of the cortex. Note the relative hypointensity of the thalami (*arrows* in **a**) and the slight white matter hyperintensity in both cerebral hemisphere with a relative sparing of the central regions. A mild global cerebellar atrophy is present and corpus callosum is very thin

Top Differential Diagnosis

Progressive neurological disorders should be considered, including leukoencephalopathies/leukodystrophies, peroxysomal disorders, mitochondriopathies, epileptic encephalopathies, Niemann-Pick, and Lafora diseases, NBIA and GM2 gangliosidosis. Visual impairment is common in some of the above diseases, retinal involvement is rare.

In juvenile- or adult-onset NCLs variants presenting with epilepsy or progressive dementia, Rasmussen syndrome, epilepsy with electric status epilepticus during slow sleep, tuberous sclerosis and Sturge-Weber syndrome should be considered. In cases presenting with typical movement disorders, Huntington disease, mitochondrial disorders, Parkinson-like diseases, and Joubert syndrome should be further considered and ruled out.

Principles of Treatment

Treatment is mainly symptomatic (e.g., antiepileptic drugs). Enzyme replacement, neural stem cell transplantation, viral vector gene therapy have been attempted.

Prognosis and Outcomes

Prognosis is generally poor. Early-onset variants have a high rate of death before 10 years of age. Adult variants frequently show a protracted course (until sixth or seventh decade). Clinical impairment is globally severe, in the late-onset variant as well, with general motor and cognitive impairment, and drug-resistant seizures. Hypomobility, malnutrition, visual and speech loss, pain, sleep disturbances, and psychiatric symptoms represent a crucial therapeutical challenge.

19.3.3 Disorders of Metal Metabolism

19.3.3.1 Menkes Disease and ATP7A-Related Disorders (MD)

Key Facts

- **Definition** – MD is part of a nosological spectrum due to a defect in copper transport and delivery due to ATPase7A gene mutations
- **Prevalence** – 1:100,000 births
- **Clinical features** – Infants: cephalohematoma, Wormian bones, prolonged jaundice, hypothermia, hypoglycemia, and feeding difficulties. At 1–2 months somatic features are typical (kinky, depigmented hair, frontal or occipital bossing, micrognathia), with developmental regression, seizure, cerebrovascular tortuosity, skeletal and urogenital abnormalities with bladder diverticula and umbilical and inguinal hernias. Children aged 2–3 years may present blindness, subdural hematoma, and respiratory failure.
- **Diagnostic markers**
  - **Blood** – Low copper and ceruloplasmin; abnormal catecholamines; molecular genetic tests
  - **MRI** – Defective myelination, vascular tortuosity, cerebral atrophy, ventriculomegaly
- **Top differential diagnosis** – Organic acidurias, biotinidase deficiency, mitochondrial and connective tissue diseases
- **Principles of treatment** – Subcutaneous injections of copper histidine or copper chloride. L-DOPA
- **Prognosis and outcomes** – Severe disability and poor survival rate in classic disease. Severely affected patients die within 3 years of age for infections, vascular and neurological complications

Definition

Menkes or "kinky hair" disease (MD) is an X-linked disease, part of a nosological spectrum [68] of defects in copper transport and delivery caused by mutations in ATPase7A gene (ATP7A, OMIM 30001, 309400, 304150). MD is characterized by a pathological continuum ranging from severe classic MD, MD intermediate phenotypes (including symptomatic female carriers), occipital horn syndrome (OHS), and X-linked distal hereditary motor neuropathy.

Prevalence

>1:100,000 births

Clinical Features

Progressive neurodegeneration and connective tissue involvement since birth are typical of severe forms. Infants may be preterm with cephalohematoma or spontaneous fracture (Wormian bones), prolonged jaundice, hypothermia, hypoglycemia and feeding difficulties, pectus excavatum, umbilical and inguinal hernias, bladder diverticula, heart valvular diseases.

At 1–2 months of age, clinical phenotype is clear and reveals typical somatic features (kinky and depigmented hair, pale skin, frontal or occipital bossing, micrognatia, puffy cheeks, Wormian bones), along with developmental regression, seizure, urogenital and skeletal abnormalities, cerebrovascular tortuosity, marked hypotonia, and joint laxity followed by spasticity and paresis.

By the age of 2–3 years, children present an often severe clinical impairment with blindness, subdural hematoma, and respiratory failure.

Most patients die within the third year due to infections, vascular complications, or severe neurological impairment.

Occipital horn syndrome mainly causes prominent connective tissue involvement with occipital exostoses, skin laxicity, inguinal hernias, hypotonia, joint hypermobility, dysautonomic, and connective tissue symptoms.

Besides the classic phenotype, the spectrum of the disease is a continuum including milder, rarer, forms [69, 70] which generally show developmental delay, variable connective tissue manifestation, ataxia, lack of seizures, and longer survival.

Symptomatic female carriers have also been reported [71].

Lastly, ATP7A gene is also responsible for an adult-onset distal motor neuropathy, which shares some features with other hereditary distal neuropathies, like Charcot-Marie-Tooth disease.

Diagnostic Markers

Blood – Serum copper and ceruloplasmin concentrations are both low. Plasma and CSF catecholamines are abnormal, reflecting a secondary dopamine beta hydroxylase dysfunction due to copper deficiency.

Cultured fibroblasts and molecular genetic analysis – Copper transport measurement in fibroblasts and genetic analysis are mandatory to detect female carriers.

Brain MRI – Defective myelination, vascular tortuosity, and cerebral atrophy together with ventriculomegaly are reported.

Brain MRI Angiography – Required to better assess the "corkscrew" aspect of cerebral vessels.

Top Differential Diagnosis

This includes other neurodevelopmental severe disorders, characterized by hypotonia and seizure (organic acidurias, biotinidase deficiency, and mitochondrial diseases). Milder forms may be similar to connective tissue protein alterations, such as elastin or fibulin mutations causing cutis laxa phenotypes.

Principle of Treatment

In classic disease and in milder forms, early subcutaneous injections of copper histidine or copper chloride has proven to be effective in many patients.

Prognosis and Outcomes

Survival rate is poor in the classic disease, with most of the patients dying around 3 years of age. Patients affected by milder forms present a longer survival rate and some can survive until adulthood (the original case [70] is now 34-years-old and other milder patients are over 50). The clinical impairment is widely different and patients, on average, experience a severely disabling syndrome with motor and cognitive impairment, and dysautonomic symptoms. Patients generally go through repetitive surgery and need chronic physical therapy.

19.3.3.2 Wilson's Disease (WD)

Key Facts

- **Definition** – WD is an AR disorder of copper metabolism due to ATPase7B gene mutation
- **Prevalence** – 1:30,000 births
- **Clinical features** – Onset between 3 and 60 years of age with hepatic, hematologic, ophthalmologic, neurologic, and psychiatric impairment
- **Diagnostic markers** – Kayser-Fleischer ring, low serum ceruloplasmin; high levels of urinary copper
  - **Liver biopsy** – Cu^{++} more than 250 mcr/g of dry tissue.
  - Molecular genetic tests
  - **MRI** – Basal ganglia T2 Hypo-hyperintensity; brainstem, cerebellar and cerebral white matter abnormalities
- **Top differential diagnosis** – Acute or chronic hepatic involvement; methanol poisoning. Kayser-Fleischer may be present in chronic cholestatic diseases
- **Principles of treatment** – Copper chelators: D-penicillamine, trientine. Zinc. Liver transplantation
- **Prognosis and outcomes** – High mortality in some severe variants: 3% of patients with fulminant course. Liver failure is the main life-threatening feature

Definition

Wilson's disease (WD, OMIM 277900) (alias: hepatolenticular degeneration or Westphal-Strumpell pseudosclerosis) is an AR disorder of copper metabolism [72] due to a mutation in the ATPase7B (ATP7B) gene, which encodes a transmembrane copper-dependent P-type ATPase.

Prevalence

1:30,000 births

Clinical Features

WD is characterized by dramatic build-up of intracellular hepatic copper with subsequent hepatic and neurologic abnormalities. Disease onset varies from the age of 3 to 60 years, with a variable combination of hepatic (fulminant, acute, or chronic hepatitis), hematologic (hemolytic anemia), ophthalmologic (corneal Kayser-Fleischer ring, sunflower cataract), neurologic, and psychiatric impairment.

The neurological picture was historically divided in four subgroups: parkinsonian, tremor and dysarthria, dystonic, and choreic movements. Psychiatric symptoms comprise early-onset neurosis, compulsive or antisocial behaviors, affective impairment, and depression. The symptomatic picture can display early-onset hepatic disease or an adolescent/adult-onset neurologic impairment, with or without liver involvement [73].

Diagnostic Markers

Laboratory

Diagnosis is suggested, by the presence of the ocular Kayser-Fleischer ring (95 % of patients with neurologic symptoms), by clinical and biochemical data showing low serum ceruloplasmin and copper concentrations, high levels of urinary copper, and increased copper hepatic concentrations.

Liver biopsy – The diagnosis is established if content of Cu is more than 250 mcr/g of dry hepatic tissue. Liver biopsy is required only if noninvasive tests do not allow to reach a final diagnosis. Molecular genetic testing confirms the diagnosis.

Brain MRI – Patients present variable degrees of basal ganglia, brainstem, cerebellar and supratentorial white matter involvement with cortical atrophy. Basal ganglia T2 hyperintensity (mainly involving the globus pallidus, bilaterally), is associated to the severity of the dystonic picture (Fig. 19.2). MRI alterations are partially reversible with a more evident effect in early treated patients [74].

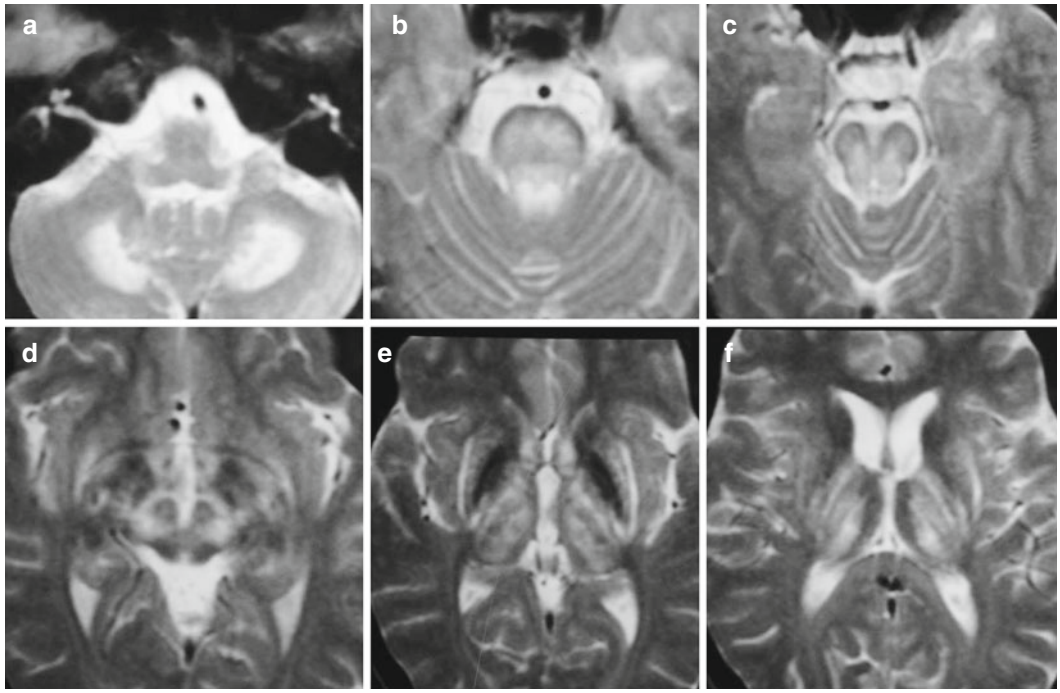

Fig. 19.2 Wilson Disease. Axial T2-weighted images, **a**-**f**, show the typical findings of the disease. Hyperintesity is observed in the cerebellar white matter, **a**, and in the pons with sparing of the peripheral profile, **b**. In the midbrain, hyperintesity with sparing of red nuclei, reticular portion of substantia nigra and superior collicula produce the so called «giant panda» sign, **d**. In the basal ganglia, E, stripes of low signal intesity are due to paramagnetic effect of the accumulation of iron, copper and hemosiderine derivates. Inhomogeneous signal intensity spared the medial profile of the thalami, **f**

Top Differential Diagnosis

Acute or chronic hepatic involvement due to viral or autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, alpha 1 antitrypsin deficiency, hereditary hemochromatosis, alcoholic and nonalcoholic steatohepatitis, and drug hepatotoxicity. Kayser-Fleischer ring may be present in patients with chronic cholestatic diseases. Hence, none of the laboratory or clinical features by itself can be considered specific for the diagnosis.

The neurological picture must be distinguished from juvenile Parkinson disease, Huntington disease, dentatorubro-pallidoluysian atrophy, dystonias, Niemann-Pick type C disease.

Principles of Treatment

Copper chelators, such as D-penicillamine and trientine, together with zinc administration, are the first choice. Neurological deterioration has been observed during the first weeks of treatment, mainly with D-penicillamine.

D-penicillamine may cause several side effects (including bone marrow toxicity). Antioxidants supplementation, mostly vitamin E and N-acetylcysteine, may reduce mitochondrial damage and lipid peroxidation. Symptomatic drug treatment for dystonia and parkinsonism are also employed.

Liver transplantation is mainly recommended in severe and nonresponsive cases.

Prognosis and Outcomes

Until 1951, Wilson's disease was a progressive and fatal disorder, with life expectancy of approximately 5 years. The introduction of copper chelators has improved clinical outcomes and prognosis although mortality is high in some severe variants. In fact, 3% of patients present a

fulminant course (mostly children) with acute liver failure as the main life-threatening feature; but also late-onset unresponsive patients have been reported. Liver transplantation can be the therapeutic option for severe complications (i.e. liver failure) of patients with WD. Indeed, data from the French cohort of patients reports a good long-term outcome [75].

19.3.3.3 Neurodegeneration with Brain Iron Accumulation (NBIA)

Key Facts

- **Definition** – NBIAs are a group of neurodegenerative disorders with characteristic deposition of iron in the basal ganglia
- **Prevalence** – 1–3: 1,000,000 births
- **Clinical features** – Early-onset variant: developmental delay, spastic/dystonic tetraparesis. Atypical late-onset, slowly progressive forms show dystonia-parkinsonism syndrome and cognitive decline
- **Diagnostic markers** – Basal ganglia iron deposits, blue histiocytes in bone marrow, molecular genetic tests
  - **MRI** – Iron deposits mostly involving the basal ganglia
- **Top differential diagnosis** – NCLs, alpha fucosidosis, Leigh syndrome, early-onset Parkinson disease, dystonia-parkinsonism syndromes
- **Treatment** – Mainly symptomatic
- **Prognosis and outcomes** – Early-onset variants have a rapid, progressive course. Late-onset forms are less severe. Outcome is generally due to severe motor and cognitive impairment

Definition

Neurodegeneration with brain iron accumulation (NBIA) comprises a group of neurodegenerative genetic disorders characterized by extrapyramidal movement disorder, intellectual deterioration, and a characteristic deposition of iron in the basal ganglia.

Distinct subtypes of neurodegeneration are defined by mutations in specific genes.

Mutations in *PANK2* and *PLA2G6* have been recognized as the most common forms of NBIA and contribute to the greatest burden of disease [76, 77].

Prevalence

1–3:1,000,000 births

Clinical Features

NBIAs include several patterns of diseases that can be divided in typical early-onset variant (characterized by developmental delay evolving toward spastic/dystonic tetraparesis) and atypical late-onset, slowly progressive forms with dystonia-parkinsonism syndrome and cognitive decline.

Diagnosis Markers

Diagnosis is mainly based on clinical suspicion, neuroimaging demonstrating iron deposits, and/or bone marrow aspiration for blue histiocytes.

Molecular genetics allows conclusive characterization.

Brain MRI – Shows images of iron deposits mostly involving basal ganglia. The "eye of the tiger" sign represents the pathognomonic feature of PKAN (Fig. 19.3). Cortical and cerebellar atrophy together with other brain stem or medullary alterations can be observed.

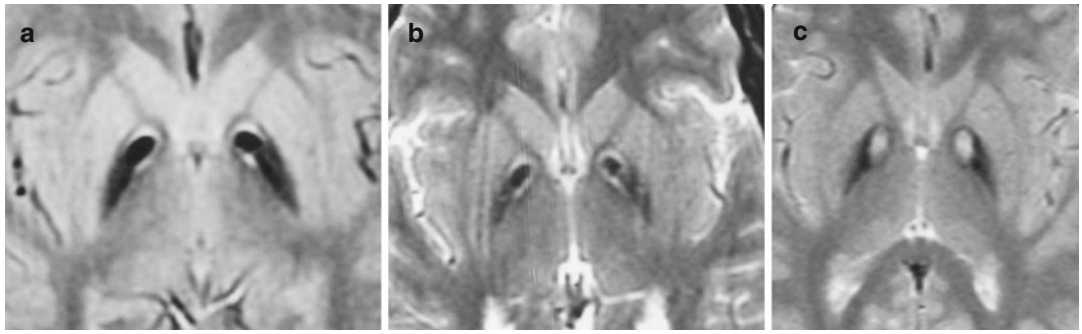

Fig. 19.3 Pantothenate kinase-associated neurodegeneration (PKAN). T2-weighted images in three different cases, **a**-**c**, show the pathognomonic finding of the disease, the "eye-of-the-tiger" sign: a central hyperintense signal in the medial portion of the globus pallidus, surrounded by hypointensity, related to iron accumulation. Central hyperintesity may include a central spot, **a** and **b**, or not, **c**, and atrophy of the pallida is always observed.

Top Differential Diagnosis

Includes NCLs, early-onset Parkinson disease, dystonia-parkinsonism syndromes, and atypical leukoencephalopathies.

Principles of Treatment

Treatment is mainly symptomatic. Iron chelators have been employed without clear efficacy. Deferiprone, a new iron chelator, which crosses the blood–brain barrier, has shown promising results, producing reduction of iron content in the globus pallidus.

Prognosis and Outcomes

Prognosis is widely variable in different neurological subtypes and generally relates to the age of onset of symptoms. Typical, early-onset variants have a severe, rapid, progressive course. Atypical and late-onset forms present a less severe clinical impairment, with death occurring only in the presence of severe dystonia, and compromised swallowing. Outcome is generally poor with a severe motor and cognitive impairment limiting daily life activities. Nevertheless, there are increasing numbers of reports concerning patients presenting a poorly symptomatic late-onset disease.

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Mitochondrial Disorders

20

Stefano DiDonato and Angelo Sghirlanzoni

Abbreviations

AD, autosomal dominant; AED, antiepileptic drug; AHS, Alpers-Huttenlocher syndrome; AHSCT, autologous hematopoietic stem cell transplantation; ANS, ataxia neuropathy spectrum; AR, autosomal recessive; CK, creatine kinase; CNS, central nervous system; CoQ10, coenzyme Q10; COX, cytochrome c oxidase; CPEO, chronic progressive external ophthalmoplegia; CSF, cerebrospinal fluid; ECG, electrocardiogram; KSS, Kearns–Sayre syndrome; L, lactate; LS, Leigh syndrome; LHON, Leber's hereditary optic neuropathy; MD, mitochondrial disorder; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MEMSA, myoclonic epilepsy myopathy and sensory ataxia; MERRF, myoclonic epilepsy with ragged red fibers; MILS, maternally inherited Leigh syndrome; MNGIE, mitochondrial neuro-gastro-intestinal encephalomyopathy; MRS, magnetic resonance spectroscopy; mtDNA, mitochondrial DNA; NARP, neuropathy ataxia and retinitis pigmentosa; nDNA, nuclear DNA; OXPHOS, oxidative phosphorylation; P, pyruvate; PEO, progressive external ophthalmoplegia; PNS, peripheral nervous system; RC, respiratory chain; RRFs, ragged red fibers; SDH, succinate dehydrogenase; VPA, valproic acid

20.1 Mitochondrial Structure and Function Relevant to Pathology

The term "mitochondrial disorders" is applied to the clinical syndromes associated with abnormalities of the common final pathway of the mitochondrial energy metabolism, i.e., oxidative phosphorylation (OXPHOS). Faulty OXPHOS is due to dysfunction of the respiratory chain (RC), the structure embedded in the inner mitochondrial membrane, formed by five hetero-multimeric complexes (complex I, II, III, IV, and V).

From the genetic standpoint, the RC is a unique structure shaped by means of complementation of two separate genetic systems: the nuclear genome (nDNA) and the mitochondrial genome (mtDNA) [1].

The nuclear genome encodes most of the 88 protein subunits of the RC complexes I to V, including the two highly hydrophobic, mobile, small electron carriers coenzyme Q10 and cytochrome c, and most of the mtDNA replication and expression systems.

The mitochondrial genome encodes 13 RC subunits, 22 mitochondrial-specific tRNAs, and 2 RNA components of the mitochondrial

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translational apparatus [2, 3]. Hence, mitochondrial disorders associated with OXPHOS defects include both *Mendelian-inherited* and cytoplasmic-maternal inherited diseases [4] (Table 20.1).

In terms of function, the RC carries out two main integrated reactions:

1. The exoergonic transfer of electron equivalents from the reduced electron carriers NADH and FADH2 to molecular oxygen (respiration, complex I-IV), a process coupled to proton translocation across the inner membrane.
2. The endoergonic ATP synthesis (phosphorylation, complex V) driven by the energy primarily stored as an electrochemical proton gradient [2, 3]. Electron transfer and ATP synthesis are coupled, or linked [3, 5], since the RC works as a proton pump which generates a proton gradient and a membrane potential of about 180 mvolts across the inner membrane and the proton gradient is utilized by the ATP synthase to phosphorylate matrix ADP. During this process the proton gradient is decreased and this activates respiration, i.e., electron transfer [3, 5].

OXPHOS diseases are mostly expressed in high-energy demanding nonmitotic tissues such as heart, skeletal muscle, and the central and peripheral nervous system [6].

The "competence" of the RC, i.e., the effectiveness of ATP generation compared to caloric intake, is called coupling efficiency and reflects both the efficiency by which complexes I, III, and IV convert the oxidation of reducing equivalents into Delta-P (membrane potential) and the efficiency by which complex V converts Delta-P into ATP. Tightly coupled OXPHOS indicates a coupling efficiency that maximizes ATP generation per calorie intake [3, 5]. Remarkably, all the *proton-translocating complexes* of OXPHOS (complexes I, III, IV, and V) must be balanced to ensure that one complex is not disproportionally permeable to protons and thus shorts Delta-P. This is achieved by having the core electron and proton transport genes retained on a single piece of *non-recombining DNA*, the exclusively maternally inherited mtDNA [3, 4].

Key Facts

- **Terminology and definitions** – Mitochondrial disorders are clinical phenotypes associated with abnormalities of OXPHOS.
- **Clinical features** – Vary from CNS involvement (encephalopathies, stroke-like episodes, seizures, ataxia, and dementia) to PNS and striated muscles deficits.
  - **Diagnostic markers**
    - **Blood** – Mildly elevated CK (muscle involvement); raised L and L/P values (disorders of OXPHOS)
    - **CSF** – Mildly elevated proteins and raised L and L/P values (CNS involvement)
    - **Genetics** – Maternal (mtDNA primary mutations); AD, AR, X-linked (primary nDNA mutations)
    - **Imaging** often not specific; stroke-like lesions (MELAS); signal abnormalities in the basal nuclei, and brainstem (LS)
    - **Muscle biopsy** – RRF (MERRF, MELAS, NARP, MNGIE); Cox-deficient fibers (MNGIE)
- **Top Differential Diagnoses** – Myastenia gravis (PEO), multiple sclerosis (LHON), metabolic encephalopathies (MERRF), metabolic and hereditary myopathies and cardiopathies
- **Prognosis**
  - **Principles of treatment** – Therapy is usually only supportive.
  - **Disability** – Most MD are chronic and progressive often causing premature death.

20.2 Terminology and Definitions

Mitochondrial disorders (MD) (alias mitochondrial encephalomyopathies, mitochondrial myopathies, oxidative phosphorylation disorders) are clinical syndromes associated with abnormalities of the common final pathway of mitochondrial energy metabolism, OXPHOS [1]. They can be caused by mutations in mitochondrial DNA (mtDNA) or in nuclear genes (nDNA).

20.3 Epidemiology

MD affect at least 1/8000 of the general population [7], but about one in 200 healthy humans harbors a pathogenic mtDNA mutation that potentially causes disease in the offspring of female carriers [8]. The risk of recurrence of MD in the offspring of an affected mother with a single mtDNA deletion is 4.11 % [9].

20.4 Clinical Features

Mitochondrial diseases most often involve the central nervous system (CNS), peripheral nervous system (PNS), and striated muscles. Affected patients, may exhibit a mixture of multiple organ dysfunctions, or deficits limited to visual impairment, e.g., Leber's hereditary optic neuropathy (LHON).

Some peculiarities of mitochondrial functioning play a crucial role in determining the clinical characteristic of mitochondrial disorders.

20.4.1 Phenotypes

Defective OXPHOS principally affects tissues with high-energy demand (central nervous system; skeletal and cardiac muscle; peripheral nerves; eye; and endocrine organs), frequently resulting in multisystem disorders [10] mainly involving post-mitotic cells and tissues. Hence, on practical grounds, a diagnostic procedure to ascertain a mitochondrial disorder should be settled as soon as we recognize in a patient a pathology affecting two or more unrelated tissues or organs with high respiratory rates [6].

20.4.2 Maternal Inheritance

Mitochondrial diseases caused by mutation of mtDNA are transmitted in a pattern of *maternal inheritance* (children of both sexes inherit only the mother's mitochondrial DNA). Nuclear gene defects can also affect mtDNA, leading to secondary mtDNA mutations that can be transmitted as autosomal dominant (AD), autosomal recessive (AR), and X-linked traits and can mimic the features of disorders caused by primary mtDNA mutations.

Mutations of mtDNA mainly cause mitochondrial diseases in adults; nuclear gene (nDNA) alterations often produce the more severe infantile phenotypes.

20.4.3 Homoplasmy/Heteroplasmy and "Phenotypic Threshold Effect"

Homoplasmy means that all copies of the mtDNA are identical. This is the common condition of normal organisms. Heteroplasmy is the presence in the cell of a mixture of normal and mutant mtDNAs. The proportion of mutant to wild-type mtDNA (amount of heteroplasmy) is a central factor in the appearance and severity of mitochondrial diseases because phenotypic expression of a genetic mtDNA defect occurs only when mutant mtDNA exceeds a *threshold level* which fluctuates in tissues, and in single affected individuals, partly explaining the clinical unpredictability of mitochondrial disorders. Besides, human tissues incorporate somatic mtDNA mutations with age, possibly sustaining age-associated mitochondrial dysfunction.

At present, the concept of heteroplasmy is still valid in pathology, though we recognize now that mitochondria are dynamic in nature [11]. As a matter of fact, any given mitochondrion is not a discrete

organelle because it will fuse or merge, soon or after in its life, with other mitochondria. Mitochondrial fusion not only results in the mixing of outer and inner membrane but also of the matrix content, *including the mitochondrial DNA* organized in the matrix in discrete units called nucleoids [3]. Fusion and the opposite event of mitochondrial splitting, dubbed fission, do not simply occur at cell division but are constant features of the cell life, so that the identity of *any mitochondrion is transient*. The relevance of this concept in mitochondrial genetics is patent as one of its major consequence is that a given mitochondrion within a *heteroplasmic cell*, i.e., a cell containing more than unique species of mitochondrial DNA, will likely contain both mutant and wild-type DNA [3, 11].

20.5 Diagnosis

20.5.1 Diagnostic Markers

Blood – Routine analysis: neutropenia, thrombocytopenia, and anemia characterize some OXPHOS disorders. Diabetes mellitus is a common feature. Creatine kinase (CK) is mildly elevated with muscle involvement. Raised lactate (L), with L/pyruvate (P) = 10–20, points to altered pyruvate metabolism; raised lactate with L/P > 20 points to disorders of oxidative phosphorylation. The amount of amino and organic acids (blood and urine), acyl-carnitines (free and total in blood and urine), coenzyme Q level (blood) may be an important clue to diagnosis.

Heart – Cardiac arrhythmias and hypertrophic cardiomyopathy should routinely be searched for.

Ears and eyes – Sensorineural hearing loss; cataracts, retinitis pigmentosa, optic neuropathy, and visual field defects are frequent features of MD.

CSF – Cerebrospinal fluid protein are increased in encephalopathies; L and P, L/P (see above).

Muscle biopsy – Routine light microscopy, immunohistochemistry. Ragged red fibers (RRFs) may be found in MERRF, MELAS, and NARP. Cytochrome oxidase deficiency may be found in LS, etc.

MRI – Can be nonspecific or reveal signal abnormalities in the lentiform and caudate nuclei, thalamus, brainstem in LS (Fig. 20.1); transient stroke-like lesions not confined to vascular territories in MELAS. T2/FLAIR: hyperintense bilateral lesions in subcortical white matter, thalamus, basal ganglia, and brainstem in KSS. Prominent leukoencephalopathy, usually sparing corpus callosum in MNGIE.

Magnetic resonance spectroscopy (MRS) – May evidentiate high level of lactate with decreased N-acetyl-L-aspartate.

Genetics – Gene sequencing is seminal to evaluate both the nuclear and mitochondrial genomes. *Findings* – Large-scale mtDNA rearrangements (KSS, progressive external ophthalmoplegia (PEO), and others); point mutations in mtDNA (MELAS, LHON, myoclonic epilepsy with ragged red fibers (MERRF), and others).

20.6 Top Differential Diagnosis

Varies from myasthenia gravis (e.g., for PEO) to multiple sclerosis (e.g., for LHON), metabolic encephalopathies (e.g., for MERRF), myopathies and cardiopathies in a variegate assembly of symptom, signs, and syndromes which require profound neurological and genetic knowledge.

20.7 Therapy

Despite the myriad of studies on the treatment of MD, effective therapy has yet to be found [12]. Treatment is usually only supportive and the large majority of MD patients are burdened with chronic progressive illnesses which often cause premature death and physical disability, with the partial exception of coenzyme Q10 (CoQ_{10}) deficiency and thymidine phosphorylase deficiency (see below).

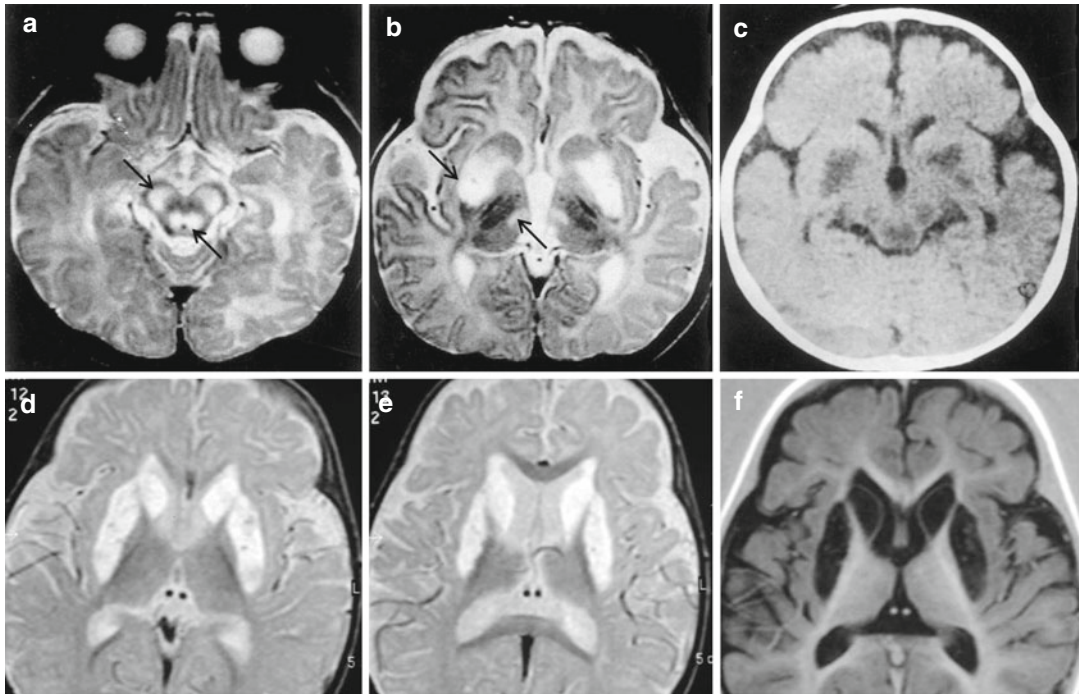

Fig. 20.1 Leigh syndrome. Two different cases. *Top*, a baby of 5 months; bottom, a child of 3 years. Top, axial T2-weighted images, (**a**, **b**), and axial CT, (**c**), demonstrate marked hyperintensities and hypodensity in cerebral peduncles, tegmen pons, bilateral putamen, and medial portion of the thalami (*arrows*). *Bottom*, axial T2-weighted images, (**d**, **e**), and axial IR image, (**f**), show necrosis of bilateral putamen and of the head of the caudate, visible as CSF cavitations of the nuclei

Exercise resistance therapy carries some help and benefit to the muscle symptoms in patients with single, large-scale mtDNA deletions [13].

20.8 Disorders Associated with a Mitochondrial DNA Mutation (Table 20.1)

20.8.1 Mitochondrial Disorders with Large-Scale Rearrangements

20.8.1.1 Chronic Progressive External Ophthalmoplegia (CPEO) and Kearns–Sayre Syndrome (KKS)

Definition

PEO is an AD or AR syndrome associated with mtDNA large-scale depletion and/or accumulation of mtDNA mutations and deletions.

Clinical Features

Onset of CPEO is between 18 and 40 years of age. Bilateral ptosis and progressive weakening of the external eye muscles characterize CPEO. Proximal muscle weakness and wasting, as well as exercise intolerance may be associated with ophthalmoparesis.

Prognosis

Clinically isolated CPEO shows slowly progressive, usually symmetrical, course over a period of 5–15 years. Autosomal recessive PEO can have an earlier onset.

20.8.1.2 Kearns–Sayre Syndrome (KSS)

Definition

Is a progressive myopathy with ophthalmoplegia and cardiomyopathy.

Large-scale mitochondrial DNA deletions or mitochondrial DNA depletion cause KKS.

Table 20.1 Mitochondrial disorders: summary of the main clinical features and prognosis [27–29]

Disease/syndrome	Clinical features	Genetics	Prognosis
Defects of mtDNA			
Chronic progressive external ophthalmoplegia syndrome (CPEO)	Mimicking KSS plus	AD; AR	Progressive disorder of variable severity, and phenotype. Onset: late teens-early 20s
Kearns–Sayre syndrome (KSS)	Slowly progressive multisystem disease, onset <20 years	Mitochondrial	Death: most often in the third-fourth decade (see text)
Leber's hereditary optic neuropathy (LHON)	Mean onset: 20 years with subacute loss of vision	Most common mtDNA mutations: 11778, 3460, 14484	Almost complete blindness in about 12 months
Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS)	Progressive neurodegenerative disorder. Onset: 2–15 years	mtDNA point mutations: A3243G (80 % of the cases)	Death: 10–35 years of age (see text)
Myoclonic epilepsy and ragged-red fiber disease (MERRF)	Myoclonus, epilepsy, ataxia, muscle weakness, deafness, and dementia. Onset: childhood or early adulthood	Mostly caused by the 8344A > G mtDNA mutation (over 80 % of the cases)	Variable, but progressive phenotype. Death: usually between 30 and 40 years of age (see text)
Neuropathy, ataxia, and retinitis pigmentosa (NARP)	Onset: childhood or early adulthood	NARP syndrome is maternally inherited. Mutated mtDNA is >95 %, patients show the maternally inherited LS	Severity depends on the mutation load. Patients may become blind, deaf, demented, and wheelchair bound
Subacute necrotizing encephalomyelopathy (Leigh syndrome/LS)	Psychomotor delay, seizures, dyspnea, ophthalmoparesis, nystagmus, vomiting. Onset: infancy or childhood (can also occur in teens and adult patients)	May be: sporadic, due to mtDNA mutations (10–30 %)	Poor prognosis: individuals typically live from a few years to mid-teens
Defects of nuclear DNA			
Myoneurogastrointestinal disorder and encephalopathy (MNGIE)	Ptosis, PEO, gastrointestinal dysmotility, neuropathy, leukoencephalopathy. Onset: late teens	AR	Most patients die before age 40 (see text)
Coenzyme Q10 deficiency disorders	Encephalomyopathy, myopathy, infantile multisystemic form, ataxic nephropatic disease, ataxic form.	AR	Variable prognosis associated with therapeutic response to coenzyme Q10 supplementation

Table 20.1 (continued)

Disease/syndrome	Clinical features	Genetics	Prognosis
Polymerase gamma mutations (POLG1 and POLG2)	AD and AR progressive external ophtalmoplegia; Alpers-Huttenlocher syndrome with epilepsy and hepatic failure; childhood myo-cerebro-hepatopathy; myoclonic epilepsy myopathy sensory ataxia (MEMSA); ataxia neuropathy spectrum (ANS) disorders	AD and AR	Poor prognosis for most POLG1 mutations with early clinical presentation (infancy and childhood). Some forms of adPEO, however, cause serious and critical neurological problems in the middle-adult age
Subacute necrotizing encephalomyelopathy (Leigh syndrome/LS)	Psychomotor delay, seizures, dyspnea, ophthalmoparesis, nystagmus, vomiting. Onset: infancy or childhood (can also occur in teens and adult patients)	May be: sporadic, or due to AD-AR, and X-linked nuclear gene mutations	Poor prognosis: individuals typically live from a few years to mid-teens

N.B.: Poor survival is usual in patients with onset of MD before 6 months of age

Clinical Features

Kearns–Sayre is a slowly progressive, usually sporadic disorder, characterized by: 1-onset before the age of 20 years, 2- progressive external ophthalmoplegia, and 3- pigmentary retinopathy (plus one among heart block, cerebellar ataxia, or CSF > 100 mg/dL).

Prognosis

In the presence of single and large-scale deletion, muscle mtDNA heteroplasmy is a significant predictor of clinical phenotype (from mild myopathy to the more severe KSS), age of onset and progression of KSS [14].

Cardiac disorders, the most important prognostic factor, affect 50 % of patients. Sudden death due to conduction defects and heart block is the major cause of mortality and occurs in 20 % of patients. The age of appearance of cardiopathy ranges between 9 and 47 years (median 28). In 69 % of the cases, syncope is the first symptom of the disease [15]. Most people die by the age of 50.

Early diagnosis, periodic electrocardiogram (ECG), and pacemaker implantation can be of great benefit in many patients.

20.8.2 Mitochondrial Disorders with Point Mutations

20.8.2.1 Leber's Hereditary Optic Neuropathy (LHON)

Definition

LHON is a maternally inherited, subacute optic atrophy with onset around the age of 20. It is caused by *homoplasmic* point mutations (see above) in the mtDNA: 11778/ND4, 3460/ND1, and 14484/ND6 are the most common mutations causing the neuropathy. In spite of mutation homoplasmy, the penetrance of the disease is incomplete, and only some mutation carriers become affected. Environmental triggers and genetic modifying factors have been considered to explain variable penetrance [16].

Impaired vision affects only 50 % of males, and 10 % of females carrying the genetic defect. Women tend to develop a more delayed, although more severe visual deficit.

Clinical Features

LHON usually begins with monocular, often painless, dimming of vision. In 25 % of cases, the second eye can be involved simultaneously; alternatively, in 75 % of patients, optic neuropathy affects the second eye with a median delay of eight weeks. The visual acuity reduction reaches its nadir within 4–6 weeks. The permanent residual visual values are often worse than 20/200 in both eyes. Central scotoma is a typical finding.

Prognosis

Visual prognosis is poor in LHON: almost complete blindness is usually certain. Visual recovery, when it occurs, generally happens between 6 and 12 months from the onset. The presence of the "14484" mutation offers a 37–71 % chance of some visual improvement, so representing the best positive prognostic factor for LHON patients; the same chance is only about 4 % in carriers of the "11778" mutation [17]. Prognosis is also better for patients with age of onset before 20 years. Perhaps idebenone gives some benefit in patients with LHON [18]. A recent finding links incomplete penetrance observed in LHON families to the efficiency of mitochondrial biogenesis: notably, asymptomatic mutation carriers were shown to carry a significant higher mtDNA cellular content, and also a greater mitochondrial mass, of their affected siblings, a key notion for future therapeutic attempts [16].

20.8.2.2 Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-Like Episodes (MELAS)

Definition

MELAS, a maternally inherited, progressive disorder has typical onset between 2 and 15 years of age. About 20 different mutations can cause MELAS. The most widespread, responsible for 80 % of the cases, is the A3243G.

Clinical Features

Typically, the stroke-like lesions can be transient, and not restricted to vascular territories.

Prognosis

Prognosis is severe. Death, due to muscle wasting, heart and kidneys disorders, or dementia occurs between 10 and 35 years of age [19].

20.8.2.3 Myoclonic Epilepsy with Ragged Red Fibers (MERRF)

In more than 80 % of the cases, MERRF is caused by the 8344A > G mtDNA mutation.

Clinical Features

The syndrome usually appears during early adulthood or adolescence and has a progressive course. Myoclonus, often the first symptom, may be followed by generalized epilepsy, ataxia, and myopathy with RRF, hearing loss, retinitis pigmentosa, and dementia.

Prognosis

The prognosis is globally poor with survival sometime limited to 30–40 years of age. The severity varies greatly and some patients, generally those with non-cerebral symptoms, may have prolonged life expectancy with relatively little handicap [20].

In treating epileptic crisis of MERRF and other mitochondrial disorders, it is essential to avoid valproic acid (VPA) or other AEDs with mitochondrion-toxic side effects.

20.8.2.4 Neurogenic Muscle Weakness, Ataxia, and Retinitis Pigmentosa (NARP)

Definition

In 90 % of cases, NARP is due to T8993G heteroplasmic point mutation in the ATPase 6 gene of mtDNA. The mutation causes NARP if present in 70–90 % of mtDNA; give rise to severe, earlier onset, maternally inherited Leigh syndrome (MILS, see below), if present in a proportion > 95 %.

Clinical Features
Symptoms of NARP usually appear in adulthood with muscle weakness, ataxia, and retinitis pigmentosa sometimes accompanied by epilepsy and mental deterioration. Ragged red fibers (RRF) can characterize muscle biopsy.

Prognosis
Severity depends on the mutation load. Patients may become blind, deaf, demented, and wheelchair bound.

20.9 Disorders Associated with a Nuclear DNA Mutation (Table 20.1)

20.9.1 Mitochondrial Neuro-Gastro-Intestinal Encephalomyopathy (MNGIE)

20.9.1.1 Definition
MNGIE is an AR disorder due to mutations in the *TYMP* gene encoding thymidine phosphorylase. A direct toxic effect of the mutations is an imbalance in the deoxynucleotide triphosphate (dNTP) cellular pool (resulting in an increased thymidine and deoxyuridine patients' tissue and blood levels and in decreased thymine and uracile availability).

20.9.1.2 Clinical Features
The syndrome is characterized by onset before 30 years of age (5 months-35 years; mean 18 years), PEO, gastrointestinal dysmotility, cachexia, polyneuropathy, leukoencephalopathy, and RRF. Cox-deficient fibers are often present in muscle biopsies.

20.9.1.3 Prognosis
The disease is relentlessly progressive and fatal with life expectancy of 20–40 years; death is commonly due to infectious or metabolic complications. However, some patients live into their sixties [21]. Innovative therapeutic approaches aimed at eliminating the toxic effects of thymidine and deoxyuridine from patients' cells, the most effective of which seems to be autologous hematopoietic stem cell transplantation (AHSCT), have been recently proposed [22]. In fact, within a group of 11 patients who underwent AHSCT, five were alive after successful transplant with full reduction of thymidine and deoxyuridine levels and clinical improvement of the gastrointestinal function, a therapeutic achievement that deserves confirmation in larger controlled studies.

20.9.2 Coenzyme Q10 Deficiency

20.9.2.1 Definition
Coenzyme Q_{10} deficiency is a phenotypically and genetically heterogeneous group of disorders.

Primary CoQ10 deficiency is an autosomal recessive syndrome due to mutations in at least five distinct nuclear genes (PDSS1, PDSS2, CoQ2, CoQ6, CoQ9, and ADKC3) involved in the biosynthesis of CoQ_{10} [23].

Secondary CoQ_{10} deficiency is associated either to primary mitochondrial DNA mutations or, more frequently, to other complex disorders such as aprataxin deficiency with oculomotor apraxia (APTX gene), and electron-transferring–flavoprotein dehydrogenase (ETFDH) deficiency with isolated myopathy and organic aciduria (ETFDH gene).

20.9.2.2 Clinical Features
The five major primary phenotypes include the encephalomyopathic form, the myopathic form, the infantile multisystemic form, the steroid-resistant nephrotic syndrome, and the cerebellar ataxic phenotype [22, 23].

20.9.2.3 Prognosis
The diagnosis of primary or secondary coenzyme Q_{10} deficiency is important because some patients may show a favorable response to oral CoQ_{10} treatment [23, 24].

Oral supplementation of 2,400 mg/day and 30 mg/kg/day doses in affected adults and children, respectively, are recommended albeit the clinical response is *de facto* unpredictable probably because treatment protocols have not been standardized [22, 23].

20.9.3 Polymerase Gamma (POLG1 Mutations)

20.9.3.1 Definition

DNA-polymerase gamma is a heterotrimer composed of one catalytic subunit (pol Gamma A, encoded by *POLG1*), containing the polymerase and exonuclease activities, and two accessory subunits (pol Gamma B, encoded by *POLG2*) thought to be important for processivity [4]. Since the first report in 2001, over 120 pathogenic mutations have been described in the gene encoding the catalytic pol γA subunit (*POLG*) [see Human DNA Polymerase Gamma Mutation Database (NIEHS Mitochondrial DNA Replication Group): http://tools.niehs.nih.gov/polg/] that are associated with a wide spectrum of mtDNA depletion or deletion neurological syndromes ranging from adult onset myopathies to severe infantile encephalopathies.

20.9.3.2 Clinical Features

Six major phenotypes are currently associated with *POLG* 1 mutations:

1. AD progressive external ophthalmoplegia (adPEO) with generalized myopathy and often variable degrees of sensorineural hearing loss, axonal neuropathy, ataxia, depression, parkinsonism, hypogonadism, and cataracts
2. AR progressive external ophthalmoplegia (arPEO) with progressive weakness of the extraocular eye muscles without associated systemic involvement
3. Alpers-Huttenlocher syndrome (AHS) with childhood-onset progressive severe encephalopathy, intractable epilepsy, and hepatic failure
4. Childhood myo-cerebro-hepatopathy spectrum (MCHS) with childhood onset, developmental delay or dementia, lactic acidosis, and myopathy
5. Myoclonic epilepsy myopathy and sensory ataxia (MEMSA)
6. Ataxia neuropathy spectrum (ANS) disorders [4]

20.9.3.3 Prognosis

Infantile and childhood forms (3 to 6 subtypes) have a quite poor prognosis both as quality of life and survival, whereas adPEO forms are relatively less dramatic disorders, in particular autosomal dominant PEO which may present as a progressive disorder in the middle-adult life that may be associated in single patients with a slow progression.

20.9.4 Subacute Necrotizing Encephalomyelopathy (Leigh Syndrome/LS)

20.9.4.1 Definition

LS can be caused by mtDNA or nDNA (AR and X-linked) mutations. Maternally inherited LS is usually due to the 8993G point mutation in the mtDNA ATP6 gene with an amount of heteroplasmy > 95 % (see NARP).

As to nuclear mutations, most mutations occur in nDNA-encoded complex I, in complex II subunits, or in mitochondrial proteins which are critic in the control of cytochrome-c- oxidase biogenesis, such as Surf1, cause Leigh syndrome [1].

20.9.4.2 Clinical Features

Classic LS is an early-onset syndrome characterized by lack of motor control, failure to thrive, seizures, generalized weakness, vomiting, irritability and continuous crying, and kidney and respiratory failure.

20.9.4.3 Pathology

The hallmark neuropathological lesions of this devastating neurodegenerative disorder of infancy or early childhood are bilaterally symmetrical foci of cystic cavitation, vascular proliferation, neuronal loss, and demyelination in the basal ganglia, brainstem, and posterior columns of the spinal cord. These lesions probably reflect the stereotypical ravages caused by defective oxidative metabolism on the developing nervous system. This concept is supported by the aforementioned notion that LS is also caused by

mtDNA mutations when they are sufficiently abundant (MILS) or severe enough to impair oxidative phosphorylation early in life [6].

20.9.4.4 Prognosis

Is generally poor. In the early-onset LS, death often occurs by age 2–3 years. About 40 % of patients die before their 20s. Onset after infancy generally means a slower progression of the disease.

Survival largely depends on the specific mutation. Pyruvate dehydrogenase and complex IV deficiency are associated with the worst prognosis. The *SURF1*-deficient LS possibly has a more favorable outcome compared to LS due to complex I-deficiency or *LRPPRC* mutations, but always within the limits of a very severe syndrome.

Age of onset before 6 months, failure to thrive, brainstem lesions, admission to intensive care units, and increased lactate in CSF are all predictors of poorer survival [25].

A recent report suggests that some cases of Leigh syndrome may favorably respond to a novel oxidative-stress modulator [26], but this lonely report needs further confirmation.

Prognosis and clinical features of the main mitochondrial neurological disorders are summarized in the table.

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Disorders of Upper and Lower Motor Neurons

21

Gabriele Mora and Adriano Chiò

Abbreviations

ALS, amyotrophic lateral sclerosis; ALSFRS-R, revised ALS Functional Rating Scale; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; ENG, electroneuronography; FTD, frontotemporal dementia; LMN, lower motor neurons; HD, Hirayama Disease; IV, invasive ventilation; MG, myasthenia gravis; MMN, multifocal motor neuropathy; MN, motor neuron; MND, motor neuron disease; MS, multiple sclerosis; MSA, multiple system atrophy; NIV, non-invasive ventilation; PEG, percutaneous endoscopic gastrostomy; PLS, primary lateral sclerosis; PMA, progressive muscular atrophy; SAP, sensory action potential; SBMA, spinal bulbar muscular atrophy; SMA, spinal muscular atrophy; SMN1, survival motor neuron 1 gene; UMN, upper motor neuron.

Motor neuron disorders are a group of diseases characterized by the degeneration of cortical motor neurons, lower motor neurons, or both, which may be secondary to various conditions, or have unknown etiology. The course can be acute or chronic progressive.

The most common clinical forms are amyotrophic lateral sclerosis (ALS), spinal bulbar muscular atrophy (SBMA or Kennedy disease), and spinal muscular atrophy (SMA).

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21.1 Amyotrophic Lateral Sclerosis (ALS)

Key Facts

- **Terminology and definitions** – Motor neurons disorders (ALS, SBMA, SMA) are a group of diseases characterized by the degeneration of cortical motor neurons, lower motor neurons, or both.
- **Clinical features** – ALS incidence in Western countries is 2–3/100,000/year; prevalence is 6–9/100,000. Clinical hallmarks: relentless, progressive degeneration of MNs with weakness, muscle wasting, and fasciculations, plus spasticity and hyperreflexia. Up to 50% of patients display frontal syndromes.
- **Diagnosis** – The diagnosis of ALS remains clinical.
  - **Blood/CSF** – Nonspecific.
  - **Genetics** – More than 20 genes are implicated in ALS; 60% of the risk is genetically determined.
  - **Imaging** – Neuroimaging as well as laboratory and pathological exams are performed to rule out other diseases.
  - **Neurophysiology** – Electromyography supports the diagnosis, showing active and chronic denervation in bulbar, upper limb, thoracic and lower limb muscles.
- **Top differential diagnoses** – Cervical radiculopathies, CIDP, MMN, MG, MS, MSA.
- **Prognosis**
  - **Principles of treatment** – No specific therapies. Riluzole prolongs survival, but only by a few months.
  - **Disability** – ALS is invariably fatal. Median survival time of patients is 2–3 years in the general population; 4–5 years if followed up in referral centers.

21.1.1 Definition

Amyotrophic lateral sclerosis (ALS) (synonyms: motor neuron disease in UK or Lou Gehrig's disease in USA) is a neurodegenerative disorder of adult life, characterized by the involvement of upper (UMN) and lower motor neurons (LMN) at spinal and bulbar levels that results in a relentlessly progressive paralysis of voluntary muscles.

After the recent discoveries of involvement of extra-motor areas associated to cognitive symptoms and of new causative genes, ALS cannot be considered a disease confined solely to the motor system anymore, but rather a syndrome due to a combination of genetic and environmental factors, characterized by a marked phenotypic and pathogenetic heterogeneity.

21.1.2 Demographics

The incidence of ALS in Western countries is between 2 to 3 cases/100,000/year in the general population. ALS prevalence is between 6 to 9/100,000 individuals [1]. The incidence of ALS has been rather constant in the last two decades. Most ALS cases are sporadic, while 5–10% of patients report a family history of the disease.

The only defined risk factors are old age and male gender (M/F 1.2 to 1.5:1).

The mean age at onset is between 60 and 68. In both genders, incidence rates increase up to a peak in the eight decade of life and decline rapidly afterwards.

The overall lifetime risk of developing ALS is about 1:400 in male and 1:500 in female.

21.1.3 Clinical Features

The clinical hallmark of ALS is the combination of UMN and LMN features which manifest with weakness, muscle wasting, and fasciculations, variably combined with spasticity, hyperreflexia, pseudobulbar affect, and other corticospinal tract signs. At the extreme of this spectrum, there are forms with a pure LMN involvement, called progressive muscular atrophy (PMA) and of pure UMN involvement, called primary lateral sclerosis (PLS). Both these forms usually have a more benign course.

21.1.3.1 Clinical Phenotypes

ALS is characterized by a marked heterogeneity in both its presentation and rate of clinical progression. Within clinical presentations, it is possible to recognize eight distinct phenotypes: classic, bulbar, flail arm, flail leg, pyramidal and respiratory, plus PMA and PLS [2].

Classic phenotype Characterized by the presence of symptoms in upper or lower limbs, without predominant pyramidal signs.

Bulbar phenotype Shows bulbar onset without spinal involvement for the first 6 months from onset. Pyramidal signs often are not present at onset but occur later.

Flail arm phenotype Characterized by progressive predominantly proximal weakness and wasting in the upper limbs. Functional involvement has to be confined to upper limbs for at least 12 months from onset.

Flail leg phenotype (also called "pseudopolyneuritic" or Patrikios syndrome) Characterized by a progressive distal onset of weakness and wasting in the lower limbs.

Pyramidal phenotype (or predominant-UMN ALS) in which clinical manifestations are dominated by pyramidal signs (mainly severe spastic para/tetraparesis), sometimes associated to pseudobulbar signs. At the same time, clear-cut signs of LMN impairment must be present.

Respiratory phenotype Characterized by a prevalent respiratory impairment at onset, with only mild spinal or bulbar signs in the first 6 months after onset.

21.1.3.2 Symptoms

About 2/3 of patients present with limb symptoms (spinal onset), while 1/3 has symptoms of bulbar dysfunction (bulbar onset). Respiratory onset accounts for 2–3% of cases. Disease onset and progression are asymmetrical. Extraocular and sphincter muscles are usually spared.

The main symptoms are weakness and fatigue. Bulbar involvement is present in most ALS patients with dysphagia and dysarthria.

Disease progression is extremely variable in every single ALS patient; each individual has his/her own progression rate, which tends to have a linear decline during the course of the disease. Death is usually due to a progressive respiratory failure often precipitated by pneumonia.

A dysexecutive syndrome or behavioral changes are found in up to 50% of patients, meeting the criteria for frontotemporal dementia (FTD) in 15% of cases [3] (see Chap. 16). There is clinical and neuropathological evidence to support the notion of ALS and FTD are extremes of a spectrum unified by TDP-43-positive, ubiquitin-positive inclusions; for this reason, they are called TDP-43 proteinopathies.

21.1.4 Diagnosis

The diagnosis of ALS remains clinical, focused on the presence of progressive UMN and LMN signs and their distribution in four regions: bulbar, upper limb, thoracic and lower limb, together with progression of symptoms.

Electromyography/electroneurography, showing active and chronic denervation in muscles of the four regions, supports the diagnosis.

Neuroimaging, laboratory and pathological exams are performed to rule out other diseases. Sometimes, slight hyperintensity along corticospinal tracts and slight hypointensity in central cortex may be noted (Fig. 21.1).

No specific biomarker of the disease is available, with the exception of mutations of ALS-related genes. Delay from onset of the disease to confirmation of the diagnosis can vary from 10 to 18 months. Such delay creates considerable distress in patients and the risk to undergo unnecessary surgery.

21.1.4.1 Main Differential Diagnosis

Cervical and thoracolumbar radiculopathies, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy

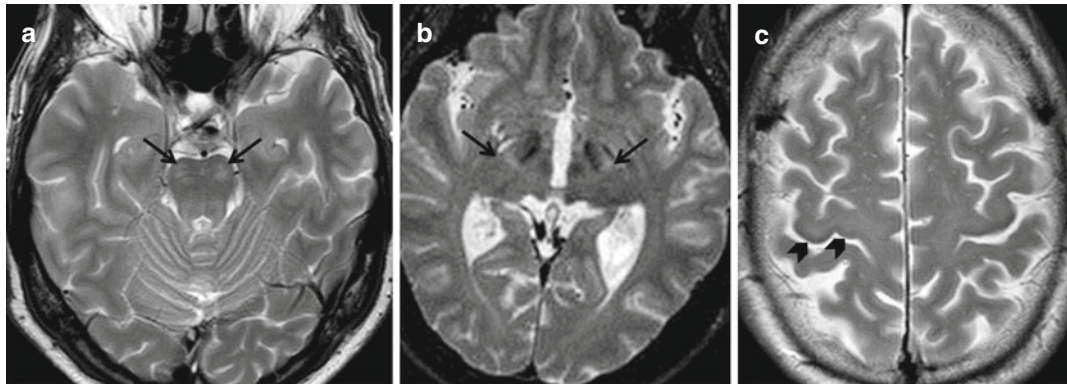

Fig. 21.1 ALS. In (**a**) and (**b**) T2-weighted images demonstrate slight hyperintensity along cortico-spinal tracts (*arrows*). In (**c**), note a slight hypointensity in both Rolando's cortex (*arrowheads*)

(MMN), myasthenia gravis (MG), multiple sclerosis (MS), multiple system atrophy (MSA).

21.1.4.2 Diagnostic Criteria

The revised El Escorial and the Awaji–Shima criteria were developed to increase the level of confidence of a diagnosis of ALS in order to facilitate inclusion criteria in clinical trials, classifying patients in different degrees of diagnostic certainty (definite, probable, probable with laboratory confirmation, possible). They both reflect the spread of the disease rather than diagnostic certainty, and therefore are not very useful in clinical practice. In fact they have been criticized because they are too restrictive, causing the exclusion of ~20–30% of ALS patients from clinical trials. Besides, they do not have a clear correlation with ALS outcome.

Genetics

Twin studies showed that about 60% of the risk of ALS is genetically determined, and the remaining 40% is environmentally determined. More than 20 genes are implicated in ALS pathogenesis. The four major ALS-related genes are *C9ORF72, SOD1, TARDBP,* and *FUS*. They account for 2/3 of familial and ~10% of apparently sporadic ALS cases [4].

In 2011, another major advance in the understanding of ALS was the identification of a large GGGGCC hexanucleotide repeat expansion in the first intron *C9ORF72* gene. This dominantly inherited condition causes both ALS and FTD. It is present in a high percentage of familial ALS and FTD, but it is also present in about 7% of apparently sporadic ALS cases. As for *TARDBP* and *FUS*, *C9ORF72* points to defective RNA processing as a central mechanism in neuronal degeneration.

Other minor ALS-related genes have roles in RNA metabolism, while some rarer forms of ALS are caused by mutations in genes involved in protein degradation pathways.

Pathology

The pathological characteristics of ALS are the presence of astrogliosis and degeneration of motor neuron cell bodies in the motor cortex, brain stem, and spinal cord. The remaining neurons contain cytoplasmic ubiquitin inclusions. In almost all cases, such inclusions stain for the protein TDP-43. Exceptions are *SOD1* and FUS-related ALS cases in whom the inclusions contain respectively SOD1 and FUS proteins abnormally aggregated. The *C9ORF72* genetic defect is associated with deposition of TDP-43 and p62, a protein involved in autophagy, in some cortical regions, and in the hippocampus. Moreover, there are ubiquitinated inclusions containing aggregates of abnormally translated dipeptide repeats derived from the hexanucleotide repeat expansion found in the cerebellum and hippocampus.

Current pathogenic hypotheses ascribe neurodegeneration to a combination of disrupted RNA metabolism and abnormal protein aggregation,

partly due to clearance failure of the proteasome system and autophagy. These mechanisms are accompanied by an immune reaction with microglial activation. Other candidate pathogenic mechanisms include glutamate excitotoxicity, oxidative stress, mitochondrial dysfunction, and failure of axonal transport [4].

21.1.5 Therapy

There are currently no specific therapies, with the exception of riluzole, which prolong survival, but only by a few months.

The mainstay of ALS management remains symptomatic treatment through a multidisciplinary approach. In the advanced phases, the use of percutaneous endoscopic gastrostomy (PEG) and of non-invasive (NIV) or invasive ventilation (IV) has demonstrated to be effective in treating malnutrition and respiratory failure.

21.1.6 Prognosis

In population-based studies, the median survival of ALS patients is 2–3 years from symptom onset, while ALS referral centers report survival times to 4–5 years [1]. There is a considerable variability in survival; in fact, about 10 % of cases survive for more than 10 years [5]. Most studies report no gender effect on ALS outcome.

Factors that predict rapid progression include an older age of onset, bulbar site of onset, short duration from first symptom to diagnosis, presence of cognitive impairment, and genotype.

21.1.6.1 Age

Age is a strong prognostic factor, and survival is inversely related to age at onset both in males and in females; older patients have a significant short survival compared to younger patients, without a gender effect [1].

21.1.6.2 Diagnostic Delay

A shorter delay from symptom onset to diagnosis (6–9 months) carries a worse prognosis. This can be explained by a more aggressive disease, with earlier neurological evaluation and diagnosis [6].

21.1.6.3 Clinical phenotypes

One study demonstrated that clinical phenotypes have significantly different prognostic characteristics [2].

PLS has a benign outcome with a median survival of more than 12 years. Also pyramidal phenotype has a relative benign prognosis, with the longest survival among ALS phenotypes, and similar to PMA. Flail arm phenotype has a median survival time of 4 years. Classic and flail leg phenotype carry an intermediate survival time. At the end of the spectrum, bulbar and respiratory phenotypes have the worst prognosis, less than 2 years. In this study, ALS phenotype was independently related to survival.

21.1.6.4 Cognitive functions

It is now clearly evident that 10 to 15% of ALS patients develop an overt FTD and that another 30–35% have a mild to moderate impairment of frontotemporal function with dysexecutive syndromes or behavioral changes. Some recent population-based studies found that patients with ALS-FTD have a shorter survival than those with normal executive and behavioral function (median survival, 28 months vs. 39 months) [7]. This difference could be explained in part to a poor compliance of these patients for procedures (PEG, NIV) in the advanced phases of the disease. A mild cognitive impairment, on the contrary, seems to have little or no effect on ALS outcome.

21.1.6.5 Nutritional status

It is widely accepted that malnourishment carries a poor prognosis in ALS. Body Mass Index is a marker of nutritional status; it has been repeatedly found to be an independent prognostic factor for death [8].

21.1.6.6 Respiratory status

Respiratory function is generally considered a critical aspect in ALS, as most patients die for respiratory failure.

Prognostic indices include: (1) percent predicted forced vital capacity; (2) upright and supine forced vital capacity; (3) percent predicted vital capacity; (4) slope of decline of vital capacity; (5) sniff nasal pressure; (6) maximal inspiratory pres-

sure and maximal expiratory pressure. All these indices were significantly correlated to survival [9].

21.1.6.7 Functional scores

The ALS Functional Rating Scale-Revised (ALSFRS-R) is the most widely used functional scale for ALS. It has been shown to be significantly related to outcome, particularly its respiratory subscore [10]. The progression rate of the ALSFRS-R, calculated as the ratio between points of score lost from disease onset to diagnosis/months of disease duration, resulted also to be significantly related to prognosis.

21.1.6.8 Multidisciplinary approach

The interdisciplinary care approach performed in tertiary ALS centers can modify patients' outcome. Increasingly, ALS patients are referred to tertiary ALS centers, whose practice is based on the interdisciplinary care paradigm. ALS patients followed by a multidisciplinary clinic have a better prognosis than those attending general neurology clinics, with a median survival from onset ~10 months longer [11]. Moreover, the hospitalization rate is markedly reduced, and the hospital stay is shorter for patients attending tertiary ALS centers. These effects were independent from all other known prognostic factors (e.g., PEG and NIV) and could be explained with a better provision of supportive care of all problems related to the disease .

21.1.6.9 Procedures

PEG is widely used for avoiding starvation and dehydration and improving quality of life. Nevertheless, whether enteral nutrition has a positive effect on survival is still a matter of debate.

NIV is the treatment of choice in the management of respiratory disturbances in ALS. One controlled trial performed in ALS demonstrated a significantly longer survival in spinal-onset patients and only a better quality of life in bulbar-onset patients [12]. A population-based study confirmed that NIV has positive effects on survival, in particular among patients followed by tertiary ALS centers compared to patients followed by general neurological clinics (316 vs 229 days) [13]. This positive effect was present also in patients with mild to moderate bulbar signs, while patients' age at the time of NIV determined a significant difference in survival (≤49, 451 days; 50–69, 268 days; ≥70, 164 days).

21.1.6.10 Genetics

Recent genotype–phenotype studies have demonstrated that gene mutations can influence age at onset and outcome [14].

Cases carrying *C9ORF72* repeat expansion have a median survival from onset of ~3 years. Patients carrying *TARDBP* mutations have a median survival of ~5 years, while *FUS* mutations are often characterized by a rapid progression and death occurring in less than 2 years.

SOD1 mutations are extremely heterogeneous in outcome. There are mutations such as the Ala4Val, which has a rapidly progressive course, whereas the Asp90Ala recessive variant is associated with a very slow course.

There are genes not causing ALS but modulating its clinical expression. They are sought with the genome wide association screening approach. The common variant rs12608932, located within an intron of UNC13A gene on chromosome 19, was found to be significantly associated with the risk of developing ALS but homozygosity for the minor allele of rs12608932 also shortens survival by approximately 12 months [15]. Another example is NI-PA1, also associated to a shorter survival.

21.1.6.11 Biomarkers

One of the most critical aspects in ALS is the lack of biological markers of disease progression to be used in clinical trials to evaluate therapeutic response.

21.1.6.12 Fluids

The search of protein biomarkers has focused mostly on blood and cerebrospinal fluid, but also on muscle and other tissues. Inflammatory cytokines and chemokines (MCP-1 and IL-8), phosphorylated neurofilament heavy chain (pNfH), CD14, S100β have been proposed but with contrasting results in terms of correlation with disease progression.

A recent population-based study in a series of ALS patients investigated several hematological markers evaluated at diagnosis [16]. Authors found

that only serum albumin, creatinine, and lymphocytes were significantly associated with ALS outcome with a dose–response effect (better survival with increasing levels) in both genders, even after correction for known prognostic factors. Serum creatinine was correlated with fat-free mass and reflects the state of muscle mass. Serum albumin was correlated with indices of inflammatory state and not with nutritional parameters, and represents a marker of chronic inflammatory state rather than of nutritional status. Sensitivity and specificity values in predicting 1-year mortality indicated that serum albumin and creatinine have properties similar to the well-established prognostic factors of ALS such as ALSFRS-R score and age. None of the other hematological factors examined – in particular lipid status and uric acid, previously reported to influence survival – were predictive of ALS outcome.

21.1.6.13 Neurophysiology

EMG signs include the presence of fibrillation potentials and positive sharp waves and enlarged motor units. However, these abnormalities do not predict disease progression.

Motor Unit Number Estimation (MUNE) is a group of techniques to estimate the number of intact motor units. It has been proposed for longitudinal assessments of motor unit death and changes in single motor unit size. However, this technique needs extensive training of healthcare staff and has a rather high test–retest variability; at present, there is no consensus about its use to follow disease progression in clinical trials.

21.1.6.14 Neuroimaging

Advanced neuroimaging techniques, being noninvasive, have considerable potential for translation into diagnostic and prognostic biomarkers [17]. If validated, these biomarkers could be easily applied into routine clinical evaluation to monitor the progression in ALS. One limit of most neuroimaging studies is that they involve small numbers of patients.

Diffusion tensor imaging and voxel-based morphometry of the cortex have revealed thinning of the primary motor cortex and degeneration in many regions including frontal lobe, corpus callosum, basal ganglia, corticospinal tract, and brainstem.

A study of magnetic resonance spectroscopic imaging (MRSI) of brain showed that ALS patients with an N-acetylaspartate/choline ratio in the motor cortex lower than 2 had a reduced survival of 19.4 months versus 31.9 of patients with a ratio over 2. If replicated in large cohorts, this observation could represent a sensitive marker of ALS outcome.

21.1.6.15 Environment

Up to date, no environmental risk factors have proven to modify prognosis in ALS [18].

21.2 Hirayama Disease

Key Facts

- **Terminology and definitions** – HD (monomelic amyotrophy) is a juvenile cervical myelopathy with a usually monolateral and auto-limited muscular atrophy of the upper extremity.
- **Clinical features** – HD is a rare disease with insidious and most often unilateral weakness and wasting of hand and forearm muscles (often C7, C8, T1 myotomes).
- **Diagnosis**
  - **Blood/CSF** – Nonspecific.
  - **Imaging** – Routine MRI is often normal. Flexion of the neck causes forward displacement of the cervical dural canal with asymmetric cervical cord flattening.
- **Neurophysiology** – Electromyography shows denervation in C7, C8, and T1 myotomes of affected limbs.
- **Top differential diagnoses** – Cervical radiculopathies, CIDP, MMN, MG, MS, MSA.
- **Principles of treatment** – Cervical collar to reduce neck flexion. Duroplasty.

  Prognosis – HD typically has a progressive course for 2–3 up to 6 years, followed by steadiness of symptoms.

21.2.1 Definition

Hirayama disease (HD) (synonym: "juvenile muscular atrophy of the unilateral upper extremity, "also known as" monomelic amyotrophy") is a rare cervical myelopathy (formerly classified as motor neuron disease by some authors) with onset in the second to third decades of life and definite male preponderance. Most cases are described in Asia, particularly Japan and India.

The pathogenesis of HD is attributed to the anterior shifting of the cervical dura mater with consequent compression of the spinal cord against the vertebral bodies when the neck is in flexion.

21.2.2 Clinical Features

Clinically, HD is characterized by the insidious onset of unilateral or bilateral asymmetric weakness and wasting of hand and forearm, without sensory or pyramidal abnormalities. In some cases, autonomic dysfunction in the involved upper extremities is reported.

21.2.3 Diagnosis

Electromyography - Shows acute and/or chronic denervation in C7, C8, and T1 myotomes in clinically affected limbs.

Cervical MRI - Is the gold standard exam for the diagnosis; it should include imaging in neutral position and imaging in neck hyperflexion. MRI reveals loss of attachment of the dura to the lamina, asymmetric lower cervical spinal cord atrophy, and forward displacement of the dura with neck flexion (Fig. 21.2).

21.2.4 Therapy

The use of a cervical collar to reduce neck flexion often prevents progressive muscular weakness. In selected cases, surgery with duraplasty and anterior cervical decompression has been proposed.

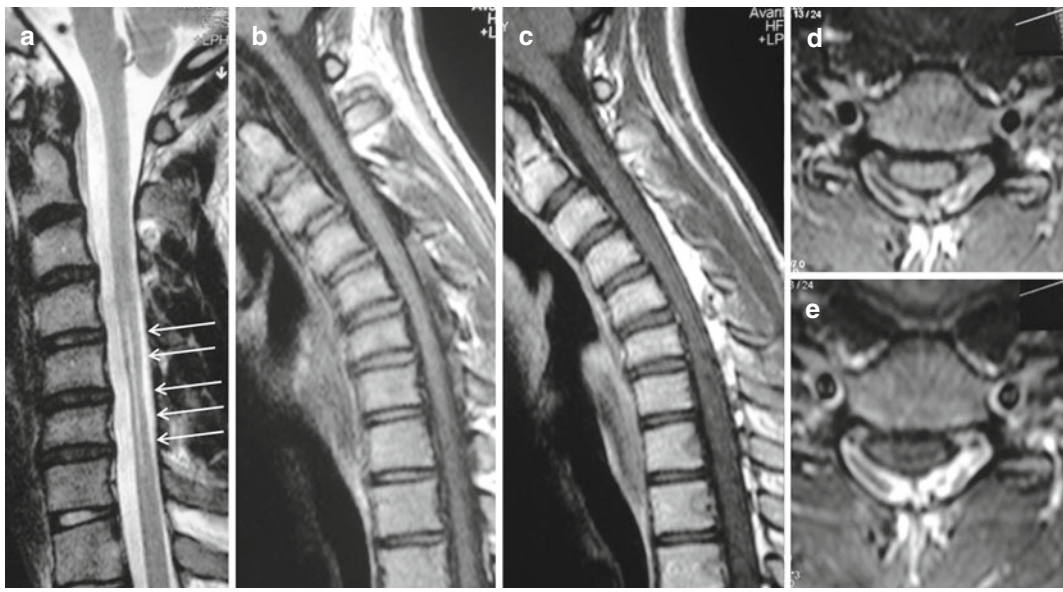

Fig. 21.2 Hirayama disease. MRI sagittal T2-weighted image, (**a**), performed 4 years after the onset of the disease, demonstrates spinal focal atrophy at C5–C6 level and hyperintense signal between C4–C7 (*arrows*). MRI sagittal and axial T1-weighted images pre- (**b**, **d**) and post-contrast medium administration (**c**, **e**) during neck flexion showing anterior displacement of the posterior dural wall and the presence of enlarged posterior epidural space with flow void images, enhancing after contrast medium administration (*arrowheads*)

21.2.5 Prognosis

Prognosis of HD is benign, and it differs from ALS because it is self-limiting. The disease has a progressive course for 2–3 up to 6 years, followed by steadiness of symptoms [19]. Nevertheless, a timely diagnosis is important to undertake early therapeutic interventions that could halt the disease.

21.3 Spinal Bulbar Muscular Atrophy

Key Facts

- **Terminology and definitions** – SBMA (Kennedy's disease) is a rare adult-onset, X-linked recessive motor neuron disease disorder, due to expansion of a CAG repeat.
- **Clinical features** – Onset usually occurs in the fifth decade with weakness and wasting in limbs and bulbar muscles. There is a variable degree of sensory nerve and endocrine involvement.
- **Diagnosis**
  - **Blood** – May show endocrine system involvement (gynecomastia, reduced fertility, diabetes)
  - **Genetics** – Males with SBMA have 38–62 CAG repeats on X chromosome, whereas individuals without the disorder have 9–36 CAG repeats.
  - **Imaging** – Neuroimaging rules out other diseases.
  - **Neurophysiology** – Fasciculations and cramps are a prominent feature. SAP can be reduced or absent.
- **Top differential diagnoses** – Cervical radiculopathies, CIDP, ALS
- **Principles of treatment** – Clenbuterol may be effective in improving motor function.
- **Prognosis** – Patients' long-term survival is only slightly reduced. CAG repeat size is significantly inversely correlated with onset and progression of the disease.

21.3.1 Definition

Spinal bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a rare adult-onset, X-linked recessive motor neuron disease disorder, caused by the expansion of a CAG repeat, giving rise to a polyglutamine tract, in the gene encoding the androgen receptor on the X chromosome. Patients with SBMA have 38–62 CAG repeats, whereas individuals without the disorder have 9–36 CAG repeats.

21.3.2 Clinical Features

Clinical onset usually occurs in the fifth decade with postural tremor and fatigability, followed by weakness and wasting in limbs and bulbar muscles. Fasciculations and cramps are a prominent feature. Patients have also variable degrees of involvement of peripheral nerve sensory system, with reduced/absent SAP at ENG, and of endocrine systems, including gynecomastia, reduced fertility, and diabetes. Most patients also have high serum concentrations of creatine kinase.

21.3.3 Diagnosis

SBMA is a rare disease, though it is possible that some patients are misdiagnosed with other neuromuscular diseases.

SBMA can mimic ALS. The main difference is that it is confined to LMN, without UMN involvement. Moreover, a genetic test can now easily confirm the diagnosis.

21.3.4 Therapy

Management of SBMA includes physiotherapy, provision of assistive devices (cane, walker, wheelchair), and evaluation of swallowing and respiratory functions. PEG is rarely performed in SBMA patients. Some patients use nocturnal NIV.

Recently, a pilot study provided Class IV evidence that clenbuterol is effective in improving motor function in SBMA.

21.3.5 Prognosis

SBMA progression is usually very slow, and patients' long-term survival is only slightly reduced compared to general population. Patients maintain a relatively good functional status years after the diagnosis. Only a minority of the patients lose their ability to perform activities of daily living independently until very late in the disease. Sometimes, severe pneumonia can occur in the advanced stages. CAG repeat size is significantly inversely correlated with onset, progression, and use of assistive devices [20].

21.4 Spinal Muscular Atrophy (SMA)

Key Facts

- **Terminology and definitions** – SMA is an autosomal recessive motor neurons disease due to a homozygous deletion of the SMN1 gene on chromosome 5q13.
- **Clinical features** – Progressive and generalized atrophy of bulbar and limbs muscles. Four clinical subtypes (Type I to Type IV) are recognized according to age at onset and type of progression.
- **Diagnosis** – The diagnosis of SMA remains clinical.
  - **Laboratory**
    - **Muscle biopsy** – Shows a pattern of "grouped fascicular atrophy."
    - **Genetics** – SMN1 test is 95% sensitive and 100% specific.
  - **Imaging** – Nonspecific.
  - **Neurophysiology** – Electromyography supports the diagnosis, showing active and chronic denervation in bulbar, upper limb, thoracic and lower limb muscles.
- **Top Differential Diagnoses** – Cervical radiculopathies, CIDP, MMN, MG, MS, MSA.
- **Prognosis**
  - **Principles of treatment** – No specific therapies available.
  - **Disability** – Death within 2 years (type I), within the second decade (type II); able to walk in adult life, and sometimes with favorable prognosis quoad vitam (Type III and Type IV).

21.4.1 Definition

Spinal muscular atrophy (SMA) is an autosomal recessive motor neuron disease, caused by a homozygous deletion of the survival motor neuron 1 gene (SMN1) on chromosome 5q13, leading to reduced SMN protein levels and a selective degeneration of spinal cord motor neurons. The SMN protein is ubiquitous, but particularly elevated in motor neurons; its activity seems to be related to the maintenance of a normal axonal transport and of the integrity of neuromuscular junction.

21.4.2 Clinical Features

Clinical features show hypotonia, generalized weakness, and atrophy of skeletal muscles. Weakness is usually symmetric and more severe in proximal muscles. Kyphoscoliosis often requires surgical or orthotic procedures. Bulbar involvement is prominent, particularly in the more severe forms, leading to malnourishment, weak cough, and aspiration pneumonia.

A classification in four clinical subtypes (Type I to Type IV) is based on age at onset and type of progression.

21.4.3 Diagnosis

EMG – Shows diffuse active denervation and motor unit action potentials of high amplitudes and long duration.

Muscle biopsy – Exhibits a distinctive pattern of "grouped fascicular atrophy" with a mosaic of groups of atrophic fibers alternated to fascicles entirely composed of hypertrophic fibers.

–*Genetic* Patients with suspected SMA should be tested for SMN1. The test is 95% sensitive and 100% specific.

21.4.4 Therapy

No medical treatment is available at present.

Promising novel therapeutic approaches are currently underway. They include compounds noted to increase SMN mRNA, gene therapy, and use of stem cells.

21.4.5 Prognosis

The phenotypic heterogeneity of SMA is striking, given the fact that patients have a defect in the same gene. There is a relation between age at onset and disease severity; an earlier onset bears a worse prognosis.

Type I disease is the most common and most severe form; the onset of the disease is before 6 months of age and death within 2 years, usually by aspiration pneumonia.

Type II disease is characterized by onset between 7 and 18 months of age. Death occurs during the second decade due to respiratory failure. In the last two decades, the multidisciplinary approach, with a careful management of respiratory, nutritive, and orthopedic problems, the use of NIV, mechanical in-exufflation, and PEG have increased significantly the outcome. Recent studies show a mean survival probability from 1 to 4 years, with outliers surviving up to 24 years [21].

Type III and Type IV have an older age at onset with slower progression. Most patients are able to walk in adult life, and some have a favorable prognosis quoad vitam.

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Headaches

22

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Abbreviations

CH, cluster headache; FHM, familial hemiplegic migraine; HC, hemicrania continua; HRQoL, health-related quality of life; HyDBS, hypothalamic deep brain stimulation; M, migraine; MO, medication overuse; NSAIDs, nonsteroidal anti-inflammatory drugs; PH, paroxysmal hemicrania; PTH, post traumatic headache; SUNCT/SUNA, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features; TACs, trigeminal autonomic cephalgias; TTH, tension-type headache

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Key Facts

- **Terminology and definitions** – Primary headaches: migraine, tension-type headache, cluster headache, and trigeminal autonomic cephalgias, and their subtypes. Secondary headaches (e.g. post traumatic headache)
- **Demographics** – Different prevalences and epidemiologic features among different primary and secondary headaches
- **Clinical features** – Pain with different characteristics, peculiar associated symptoms in primary headaches; warning symptoms: suspect of secondary headaches
- **Diagnosis** – Only clinical. Warning signs induce the suspect of secondary headaches
  - **Laboratory, imaging, neurophysiology** – Normal in primary headaches; may be abnormal in secondary headaches
  - **Top differential diagnoses** – Different forms of primary headaches (migraine, tension-type headache, cluster headache, and other trigeminal autonomic cephalgias); several secondary headaches
- **Prognosis**
  - **Principles of treatment** – Symptomatic treatment and prophylaxis with different drugs in primary headaches, according to the specific causative disorder in secondary headaches
  - **Disability** – Relevant in primary headaches, according to the specific causative disorder in secondary headaches
  - **Risk factors for long-term prognosis**: Several demographic, clinical, or pharmacological factors may cause a poor outcome in primary headaches, according to the specific causative disorder in secondary headaches

22.1 Primary and Secondary Headaches

22.1.1 Terminology and Definitions

Headache is one of the most common symptoms in the primary care setting as well among patients referred to neurology and emergency services [1, 2].

Primary headache is not associated with underlying pathology. Diagnostic criteria are based on the most important characteristics of pain, and of associated symptoms.

Secondary headache in which head pain is a symptom of another disease.

22.1.2 Notes on Clinical Features, Differential Diagnoses, and Prognosis of Headaches in General

Key Points [2, 3]

- Headache is a nonspecific symptom.
- 13–18 % of patients presenting to an emergency department with secondary headaches have a dangerous or life-threatening disorder.
- For primary headaches, specific drugs to relieve and to prevent headaches are available.
- Secondary headache therapy is based on the treatment of the underlying disorder.
- The prognosis of primary headaches is generally favorable.

Some primary forms may have a disabling clinical presentation, particularly if chronic, with remarkable impairment in functioning in work and nonwork duties.

Warning Signs or "Red Flags" Relevant in Suspecting a Secondary Headache [1, 2]

- Abnormal findings on neurological examination or presence of other neurological symptoms:
  - New focal neurological symptoms or signs, and/or epileptic seizure
  - Papilloedema and/or visual disturbances other than typical aura
  - Confusion and alterations in consciousness, memory, personality change
- *Abnormal findings or signs on general examination, particularly*
  - Fever
  - Neck stiffness
  - Jaw claudication

- *History of*
  - Cancer
  - Immunosuppression
- *Headache aggravated or triggered by*
  - Exertion, sexual activity, Valsalva-like maneuver
  - Changes in body posture
- The worst headache in a subject's life and/or severe headache of abrupt onset (thunderclap headache)
- Significant worsening of headache frequency or duration
- New headache in a patient over 50 years

22.1.3 Laboratory Test, CSF, Imaging, Neurophysiology in Headaches in General

The diagnosis of any primary headache is based on history and clinical evaluations. Diagnostic tests should be prescribed to rule out secondary headaches.

22.2 Migraine

22.2.1 Terminology and Definitions [2]

- *Aura*: One or more reversible central neurological system symptoms, which can be associated to migraine (M)
- *Episodic M*: The most common M subtypes, that is, M without aura and M with aura, which are characterized by headaches occurring on less than 15 days/month, presenting in attacks separated by symptom-free periods
- *Chronic M*: The M subtype in which headache is present on 15 or more days/month, often with daily or nearly daily course
- *Medication overuse* (MO): Excessive consumption (10 or 15 days/month, or more) of symptomatic drugs for headache

22.2.2 Demographics [3]

M is a common neurological disorder, with a high prevalence worldwide.

Key Points in M Epidemiology

- 1-year prevalence of episodic M around 14.7 %
- M with aura has a lower prevalence (1–4 % in men, 3–10 % in women) than M without aura
- 1-year prevalence of chronic M ranges from 1.4 to 4 %
- Incidence and prevalence of M are generally higher in young adults
- Clear female preponderance (female:male ratio 2.5–3:1)
- Age of onset: Generally before 40 years, often in childhood in men and with menarche in women; unusual after the age of 45–50 years.

22.2.3 Clinical Features and Diagnosis [2–5]

22.2.3.1 Episodic M

M without aura: Characterized by the presence of the headache phase and of associated symptoms. The diagnosis requires a duration of attacks of 4–72 h; the presence of at least two of the typical features (i.e. unilateral location of pain, pulsating quality, moderate/severe pain, aggravation by routine physical activities); the presence of nausea or vomiting, and/or photophobia plus phonophobia is mandatory.

M with aura: Characterized by aura symptoms, the most common being visual symptoms, sensory symptoms, and speech disturbances. Pain follows aura; in some attacks, headache is absent.

Infrequent, atypical auras include the following.

- *Basilar-type M* (or M with brainstem aura): Presence of at least two aura symptoms among dysarthria, vertigo, tinnitus, hypoacusis, diplopia, ataxia, and decreased level of consciousness.
- *Hemiplegic M:* Aura with motor weakness with possible different degrees of gravity; the only M form for which a genetic origin has been demonstrated (familial hemiplegic M, FHM); three genetic subtypes have been identified: FHM1, with mutations in the CACNA1A gene on chromosome 19; FHM2, with mutations in the ATP1A2 gene on

chromosome 1; FHM3, with mutations in the SCN1A gene on chromosome 2; sporadic cases are also possible.
- *Retinal M*: Very rare; aura with transient monocular symptoms, which may vary from scintillations and blind scotomata to monocular visual loss.

22.2.3.2 Chronic M

Chronic M (previously defined "transformed M," and included among the so-called "chronic daily headaches"): The main diagnostic requirement is the presence of headache on ≥15 days/month for at least 3 months. The progression from episodic M is generally insidious over months or years. The most recent diagnostic criteria allow the diagnosis of "chronic M" when headache has M characteristics on at least 8 days per month.

22.2.3.3 Medication Overuse (MO) Headache

Medication Overuse (MO) headache: The diagnosis of MO should be added to that of chronic M in patients with the use of triptans and formulations containing ergotamine or opioids on ≥10 days/month on a regular basis for more than 3 months; use of nonsteroidal anti-inflammatory drugs (NSAIDs) or simple analgesics, or any combination of different symptomatic drugs, on ≥15 days/month, on a regular basis for more than 3 months.

Relevant risk factors for progression from episodic to chronic M [4, 6]

- Female sex
- Stressful life events (such as being divorced, employment changes, problems with children, moving, etc.)
- Head injury
- Low-income levels
- Presence of comorbidities, both psychiatric (depression and anxiety) and somatic (chronic pain syndromes, hypertension, sleep disorders, etc.) disorders
- Obesity or high body mass index
- Caffeine consumption
- Baseline headache frequency
- Presence of MO

22.2.4 Prognosis

22.2.4.1 Disability [7–9]

M is a disabling disorder, with a relevant burden on individuals and on society as a whole. Estimated annual costs: 1.222 € per case, more than 90 % being indirect costs due to reduced productivity. M is ranked as the third most prevalent disorder and seventh highest specific cause of disability worldwide, in terms of years spent with disability. Several studies on clinical and population samples with standard tools showed that M has a pervasive effect on the ability to function and on health-related quality of life (HRQoL).

Key Points About the Impact of M

- Episodic M causes relevant difficulties in daily functioning during attacks in several areas, mainly in communication, mobility, self-care, participation in society, relationships with others, and with family members.
- All activities are impaired: Household activities, social, and familial duties (the most impaired); workplace activities (more in terms of presenteeism, that is, working with headache and with significant reduction in productivity, than of absenteeism); the mean number of days with disability in nonworking activities is around 20 days versus around 8 days in working activities, 1–2 of which were missed workdays in clinical samples.
- M causes a poor HRQoL also between attacks, and migraineurs' quality of life perception is significantly worse than that found in age-matched and gender-matched controls.
- The HRQoL domains that are more influenced are those evaluating social functioning, vitality, mental health, and physical health.
- "Chronic M" has a more evident and pervasive impact than "episodic M" forms, with higher levels of disability (around threefold disability scores), and more evident HRQoL reduction than other headache forms, particularly in patients with MO.

22.2.5 Treatment

The heterogeneous presentation of M implies that treatment should be tailored to the individual patient.

22.2.5.1 Treatment of Episodic M

Nonpharmacological Interventions Promoting awareness and education about the possible trigger factors may have a positive impact on M frequency and severity, as some nonpharmacological approaches (cognitive therapy, biofeedback training, acupuncture).

Symptomatic (or Acute) Treatment [10]

Triptans

- Serotonin 5-HT1B/1D receptor agonists
- All the drugs in this class have level A recommendation

NSAIDs and analgesics

- The most effective are: ibuprofen, diclofenac, naproxen, acetylsalicylic acid, paracetamol (acetaminophen).

Other drugs

- *Antiemetics*: Should be suggested to patients with regular vomiting;
- *Combinations*: Fixed associations of NSAIDS/analgesics and/or caffeine and antiemetics can be used in some patients
- *Opioids*: Should be avoided in M

Prophylaxis [5, 10]

The general principles of prophylaxis in subjects with M are reported in Table 22.1.

Drugs with a proven evidence:

- *Propranolol*: Daily doses 40–240, the most commonly effective – and well-tolerated – being 80–120 mg daily
- *Divalproex/sodium valproate*: Daily doses 500–1500 mg
- *Topiramate*: Should be initiated at 25 mg per day, with gradual titration up to 100 mg, and up to 200 if necessary
- *Amitriptyline*: Daily doses 15–50 mg
- *Flunarizine*: Suggested daily dose 5 mg

Table 22.1 General principles of prophylaxis in subjects with M and TTH

Prophylaxis should be considered in patients who report two or more of the following conditions:
High frequency (4 or more M days/month; very frequent or chronic TTH)
Unsatisfactory response to symptomatic treatment of M or of TTH
Increasing use of symptomatic drugs with the risk of MO
Significant impact on well-being and functioning in work and nonwork activities, for M or TTH
Duration of treatment: Each drug should be used for at least 2–3 months

22.2.5.2 Treatment of Chronic M [11–14]

Prophylaxis All the drugs recommended in episodic M can also be commonly used in chronic M. Specific evidence exists for the following drugs.

- *Topiramate*: Starting dose of 25 mg/day; final doses 100–200 mg/day
- *OnabotulinumtoxinA*: Administered with a standard injection paradigm; toxin injected bilaterally in suggested sites of the head and neck; total dose 155–195 U; intervals of administration of 12 weeks

Nonpharmacological Interventions Education about the possible trigger factors and information about the risks of MO are essential components in the therapy of chronic M, as well as specific approaches: biofeedback training, cognitive behavioral therapy, physical exercise programs, and relaxation training.

Withdrawal of Overused Medications This is the initial step for those who present with MO. It can be performed as an outpatient or as an inpatient (in patients with overuse of multiple drugs, drug dependence, or psychiatric comorbidities) protocol.

Key Steps in Inpatient Withdrawal Programs

- Intravenous infusion of fluids and/or antiemetics and anxiolytics.
- Abrupt stop of the overused drugs (general suggestion).

- Slow tapering down of drugs containing opioids or butalbital – or the prescription of clonidine patch to prevent opioid withdrawal symptoms, and of phenobarbital to prevent butalbital withdrawal seizures.

22.2.5.3 Risk Factors for Chronification and Long-Term Prognosis [4, 6, 12–17]

The course of M may be very different in different subjects. Episodic M forms generally tend to improve after 50 years of age and/or after menopause in women. M with aura tends to have a more evident progressive reduction in frequency of attacks, which can disappear after the age of 50, or can be limited to a short aura without headache.

However, in a minority of cases, a progressive worsening leads to the development of chronic M. As discussed in previous paragraphs, several clinical and population studies are concordant in identifying various factors potentially involved in the poor outcome of M. Among these risk factors for progression from episodic to chronic M, the potentially modifiable factors are the presence of psychiatric or somatic comorbidities (such as obesity, depression, anxiety, chronic pain syndromes, hypertension, sleep disorders, etc.), the presence of MO, and a high headache frequency [4, 15]. Baseline M frequency appeared as the strongest predictor in the few available population-based, prospective, long-term studies. In a European study in which 64 subjects with episodic M from a sample of 740 subjects were examined in 1989, and then reexamined in 2001, M remission was found in 42 %; low M frequency in 38 %; progression to chronic M in 20 %; and this poor outcome was associated with high frequency at baseline, together with age at onset <20 years [14].

Data from a US survey with a 1-year follow-up suggest that around 10 % of migraineurs experience a complete remission of 3 % a partial remission, and that 3 % progress to chronic M [4].

Thus, an appropriate management of episodic M is likely to reduce the rates of chronification. Prescription of specific treatments (prophylaxis drugs, nonpharmacological interventions), strategies to prevent MO, together with the optimal control of the earlier-listed comorbidities, must be encouraged.

Several literature reports suggest that the global impact of M can be contrasted by appropriate therapy. Controlled studies found evidence of improvement in daily functioning and in HRQoL after treatment, particularly after topiramate administration (both in patients with episodic and chronic M), and after onabotulinumtoxinA in chronic M [12, 13].

In those patients who have already progressed to chronic M, education and nonpharmacological interventions – particularly behavioral approaches – are crucial, together with the introduction of a (new) pharmacological prophylaxis.

All patients with MO should be encouraged to discontinue their overuse and to seek medical consultation. In fact, though published data about the long-term prognosis after withdrawal programs are different across studies, overall, success of treatment is likely in most cases. The relapse rate of MO may be around 30 % after 1 year (range, 14–41 % according to published studies) [12]. Higher rates of improvement are likely to occur in chronic M patients followed in headache centers: the percentage of chronic M patients reverting to episodic M over 1 year in a specialty clinic follow-up was 70 %, while it was 26 % in a population survey over 2 years [6, 17]. A significant improvement on headache days per month, symptomatic medication consumption, and disability was observed in a sample of chronic M patients followed during a 3-year inpatient withdrawal program [14].

22.3 Tension-Type Headache

22.3.1 Terminology and Definitions [2]

Terms used in the past: "Muscle contraction" or "muscle tension" headache, "psychogenic headache," etc. Tension-type headache (TTH) is now recognized as a distinct primary headache form.

- *Episodic TTH*: The most common subtype, characterized by headache occurring on less

than 15 days/month, in attacks separated by symptom-free periods.
- *Chronic TTH*: Headache is present with daily or nearly daily course.
- *Medication overuse (MO)*: The excessive (10 or 15 days/month, or more) consumption of symptomatic drugs for headache.

22.3.2 Demographics

Key Points in TTH Epidemiology [2, 18]

- Overall, TTH appears as the most frequent primary headache
- Episodic forms are most prevalent than chronic forms
- One-year prevalence is estimated around 60 % for all forms, around 2–5 % for chronic TTH
- TTH shows a slight female preponderance (female:male ratio around 5:4)

22.3.3 Clinical Features and Diagnosis [2, 18]

The different TTH subtypes are characterized mainly on the basis of frequency.

Episodic TTH: It includes infrequent episodic TTH, with attacks on <1 day/month (<12 days/year), and frequent episodic TTH, with attacks on 1–14 days/month (<180 days/year).

Chronic TTH: Headache may be unremitting for weeks to months, or even daily; diagnosis requires headaches on ≥15 days/month on average for >3 months (≥180 days/year).

Headache characteristics required for diagnosis are similar for all TTH subtypes: pain duration from 30 min to 7 days; presence of at least two of the following: bilateral location of pain; pressing or tightening (nonpulsating) quality; mild to moderate intensity; no aggravation by routine physical activity. The diagnostic requirements are somewhat different for associated symptoms: difficulty in concentration, limitation of neck movement or stiffness of pericranial muscles may be present in all forms; only one of photophobia or phonophobia is accepted for the diagnosis of the episodic forms; no more than one among photophobia, phonophobia, or mild nausea for chronic TTH.

Chronic TTH is the most severe form, and evolves from episodic TTH.

22.3.4 Prognosis

22.3.4.1 Disability [18–20]

The impact of TTH on sufferers and on society has not been so extensively studied as in M. Infrequent episodic TTH has usually no or minimal functional consequences, while frequent episodic and chronic forms may impair social activities in around 50–60 % of subjects, causing decreased work effectiveness, with one-fifth of patients missing work.

22.3.5 Treatment

22.3.5.1 Nonpharmacological Interventions

Acupuncture, physiotherapy, massage, TENS, and trigger point injection, are relatively common, though evidence for their effectiveness is not definitive. Behavioral treatments, relaxation training, biofeedback, and cognitive therapy were found to lead to significant reductions in TTH, with a response rate ranging from 30 to 60 %.

22.3.5.2 Symptomatic (or Acute) Treatment [18, 20]

NSAIDs and Analgesics

- Drugs of first choice, mainly in chronic TTH, with percentages around 15–40 % of pain-free response after hours.
- The most effective compounds are: ibuprofen, ketoprofen, diclofenac, naproxen, acetylsalicylic acid, paracetamol (acetaminophen)

22.3.5.3 Prophylaxis [18, 20]

Only a few drugs have been tested in placebo-controlled studies in TTH prophylaxis, and

their efficacy in clinical practice is often modest.

- *Amitriptyline*: The drug of first choice; started at low dosages (10 mg/day) and slowly titrated to a maintenance dose of 30–75 mg/day, 1–2 h before bedtime
- *Mirtazapine*: Second choice drug; usual daily dose 30 mg, 1–2 h before bedtime; side effects: drowsiness, weight gain

The *general principles of prophylaxis* in TTH are reported in Table 22.1

22.3.5.4 Risk Factors for Chronification and Long-Term Prognosis [15, 18]

Episodic TTH generally has a favorable prognosis, though in some subjects a poor outcome is possible. Chronification of TTH may be related to several risk factors. As discussed for chronic M, a significant association with chronification is generally found for female sex, obesity, high baseline headache frequency, as well as low education level and divorce [4]. In a population study, 146 subjects with frequent episodic TTH and 15 with chronic TTH were examined in 1989, and then in 2001. Among them, 45 % experienced headache remission or infrequent episodic TTH or remission, 39 % had frequent episodic TTH, and 16 % presented with a chronic TTH. When the possible variables for poor outcome were analyzed, baseline chronic TTH, coexisting M, not being married, and sleep disorders were the most common predictors for poor outcome [15].

It is therefore likely that an appropriate management of episodic TTH may prevent headache chronification. The available nonpharmacological interventions (particularly among the behavioral approaches) can be very useful, together with pharmacological prophylaxis, when indicated. The most used drugs for TTH prophylaxis (amitriptyline and mirtazapine) may in fact be effective also in reducing some of the above-mentioned conditions.

Avoidance of frequent use of symptomatic drugs, particularly in those with chronic TTH, must be suggested: MO (as in chronic M patients) is likely to enhance disability and to further promote headache chronification. In patients with MO, specific withdrawal programs are warranted to discontinue overuse (see Sect. 22.2.5.2).

22.4 Cluster Headache and Other Trigeminal Autonomic Cephalgias

22.4.1 Terminology and Definitions [2]

- *Trigeminal autonomic cephalgias (TACs)*: Group of primary headaches which share a strictly lateralized, orbitotemporal, short-lasting attacks of severe pain and a series of typical ipsilateral autonomic features
- *Cluster headache (CH)*: The most common of TACs; the term derives from the prominent feature, which is the recurrence of attacks typically presenting durin.g periods of weeks or months followed by remission phases

22.4.2 Demographics [3, 22]

CH is a relatively rare disorder with respect to M and TTH, and the other TACs are even more uncommon

Key Points

- Life time prevalence: 0.03–0.124 %
- 1-year prevalence: 53 per 100,000
- The prevalence of CH is higher in men; male:female ratio ranging from 3 to 7:1, and possibly being as high as 15:1 in chronic CH
- Onset of CH is usually between the third and fourth decades of life, but it is reported at any age
- Hemicrania continua (HC) and paroxysmal hemicrania (PH) are characterized by female prevalence

22.4.3 Clinical Features and Diagnosis [2, 22]

CH Attacks are stereotyped in the individual patient, with a side-locked recurrence, only a minority (10–15 %) of patients reporting a side shift. The attack has a rapid/abrupt onset and cessation, with an average duration of 45–90 min (diagnostic requirement: 15–180 min). It is a severe, even excruciating pain. Associated features: conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, miosis and/or ptosis, forehead and facial sweating, forehead and facial flushing, sensation of fullness in the ear (at least one of them must be present to make a diagnosis). Agitation and restlessness during attacks are included in the diagnostic criteria, and this typical behavior can be accepted as the only accompanying symptom to make diagnosis.

The different CH subtypes are characterized mainly on the basis of frequency.

Episodic CH Presents with active periods (or cluster bouts); diagnostic requirement: frequency of attacks between one every other day and eight per day for more than half of the time; remissions for at least 1 month, up to even several years The rhythmic character of CH is typical: often, the attacks are at a fixed time, during the day or night.

Chronic CH is characterized by the absence of remission periods or by very short intervals, less than 1 month. It usually evolves from episodic CH, but may be chronic ab initio in a minority of cases.

Other TACs PH, HC, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features (SUNCT/SUNA) are very rare. Attacks differ from those of CH, mainly for the duration and/or frequency of attacks. Female prevalence and indomethacin responsiveness distinguish.

PH and HC

22.4.4 Prognosis

22.4.4.1 Disability [21–23]

Pain in CH is very severe; patients are unable to lie down; and the frequent occurrence during sleep may cause disruption of daily activities and fatigue. Overall, CH causes a relevant burden on daily functioning during active periods and in those patients with chronic CH. Almost 20 % of CH subjects evaluated in a recent Website survey had lost a full-time employment due to CH, and 15 % of men and 24 % of women could not leave their homes for 31 days or more per year. Impairment in noneconomic and economic domains is particularly evident in patients with chronic CH, as well as psychiatric comorbidities. Lower HRQoL scores than those found in the general population are reported in episodic CH and in chronic CH patients, even when appropriate treatments are used.

Most patients with other TACs, and particularly those with SUNA/SUNCT, are remarkably disabled, due to the severity of pain attacks and to their high daily recurrence.

22.4.5 Treatment [24]

22.4.5.1 Symptomatic (or Acute) Treatment

- *Sumatriptan 6 mg, subcutaneous*: Treatment of choice for CH attacks, up to two times daily
- *Other triptans*: Sumatriptan 20 mg and zolmitriptan 10 mg nasal spray may provide adequate relief at 30 min in some CH patients
- *Oxygen*: High-flow 100 % oxygen inhalation, 10–12 L/min for 15' with facial mask; alternative to subcutaneous sumatriptan for those patients with contraindications

22.4.5.2 Prophylaxis

- *Verapamil*: This is the first choice drug for both episodic and chronic CH; it can provide 50 % reduction or more in CH attack frequency in 80 % of patients; second choice in SUNCT/SUNA, and in PH

- *Lithium carbonate*: Starting dose 300 mg daily, slow increase up to 1220–1600 mg/day in episodic CH, to 900–12,290 mg/day in chronic CH – as well as in SUNCT/SUNA; may be used also in combination with verapamil
- *Indomethacin*: First choice treatment in PH and HC (50–250 mg in three or more daily doses); a diagnostic/therapeutic trial (*indotest*) should be performed: oral trial with 150 mg divided in three to six doses, with usual positive response within 24 h, or intramuscular administration of 50–100 mg, with response within 1–1.5 h;
- *Lamotrigine*: First choice treatment in SUNCT/SUNA; daily doses: from 100 to 300 mg, starting with 25 mg/day, with a slow increase

22.4.5.3 Transitional Therapy

In high-frequency episodic CH or in chronic CH, the so-called transitional therapy or "short-term prophylaxis" can be used to give a rapid relief while waiting to establish the efficacy of prophylaxis.

- *Corticosteroids*: For example, dexamethasone 8 mg for 3 days and 4 mg for another 3 days iv or im; oral prednisone 60–100 mg/day for 5–7 days, tapering in 7–14 days;
- *Anesthetic blockade of the greater occipital nerve*

22.4.5.4 Neurostimulation [25, 26]

It should be considered in chronic, severe, and drug-resistant patients. Hypothalamic deep brain stimulation (HyDBS) has an overall successful rate of >50 % improvement in CH attacks up to pain-free in around 50–60 % of those cases, with confirmation of efficacy and tolerability with follow-ups of several years. HyDBS has been found effective in a few patients with TACs other than CH (SUNCT, PH). Occipital nerve stimulation may be effective at least as, if not superior to, HyDBS, with reported success rates around 60 %, and with no major risks.

22.4.5.5 Risk Factors for Chronification and Long-Term Prognosis [2, 27, 28]

Generally, CH is considered as a lifelong disorder. Available data about the natural history of the disease and the possible factors leading to a negative evolution of CH are sparse.

The proportion of patients having a chronic temporal pattern without remissions, that is, the worst CH clinical presentations, is estimated as 10–15 %. An observational study in 1991 [27] described a 10-year course in 189 CH patients: 13 % of the episodic form evolved into a chronic CH (chronification), while one-third of the chronic CH reverted to episodic CH, the pattern remaining rather stable in the great majority (80.7 %). The possible predictive factors for chronification were specifically investigated [28]: among several clinical, epidemiological, and behavioral variables, age at onset of CH from the third decade of life onward, having more than one cluster period a year, and the short-lived duration of remissions appeared as the main possible predictors or putative risk factors for development of chronic CH. Also, a possible role of head injury, cigarette smoking, and alcohol consumption in the evolution of the disorder was also suggested.

In clinical practice, repeated steroid cycles performed as transitional therapy or add-on therapy seem to promote CH chronification; this could simply reflect the refractoriness to repeated treatment trials in patients who are in fact progressing from severe episodic to chronic CH. Also, the risk that some patients may develop steroid dependence should be taken into account, as tapering may be difficult because of possible (partial) worsening and/or emotional problems related to this possible issue.

Though no specific research has demonstrated a clear effect of therapy in the prognosis of CH and of the other TACs, patients should be carefully followed and treated with symptomatic treatment, and, most importantly, with the available prophylaxis.

Pharmacological prophylaxis (and of the new neurostimulation approaches in a subset of particularly severe forms) may reduce the relevant burden, and lead to a favorable (at least short-term) prognosis in patients with TACs, who are generally characterized by a relevant suffering due to the severe pain attacks and to their daily recurrence for periods of months/years.

22.5 Posttraumatic (or Postconcussive) Headache

Posttraumatic headache (PTH) is one of the most common secondary headaches.

Key Points in the Epidemiology of PTH [3, 29] Prospective surveys indicate a cumulative incidence of 91 % over 1 year, as most subjects reported the onset of a new headache (or worsening of preexisting primary headaches) after injury: 54 % immediately after trauma, 62 % at 3 months, 69 % at 6 months, and 58 % at 1 year.

- PTH is more prevalent after mild traumatic brain injuries than after more severe events.

22.5.1 Clinical Features and Diagnosis [3, 29, 30]

PTH is a headache that occurs for the first time in close temporal relation to injury to the head and/or neck. There are no specific features to distinguish PTH from other headache types: most patients report the typical symptoms of primary headaches, more often of M and TTH (49 % and 40 %, respectively, in a recent prospective survey). A preexisting primary headache may worsen, and may become chronic, after trauma.

International diagnostic criteria require that headache must be reported to have developed within 7 days of trauma or injury, or within 7 days after regaining consciousness and/or the ability to report pain. This 7-day interval is somewhat arbitrary: in fact, that headache may start after longer intervals in some patients, up to 1 year from the head or neck injury.

PTH subtypes are defined based on the temporal relation between trauma and headache onset: *acute PTH*, lasting less than 3 months; *persistent (formerly chronic) PTH* if they continue beyond 3 months.

22.5.2 Prognosis

22.5.2.1 Disability [3, 29, 30]

Persistent (or chronic) PTH may cause impairment in daily functioning. Impairment is generally higher when PTH occurs as one of several symptoms of the postconcussion syndrome, such as dizziness, memory problems, reduced concentration, fatigue, personality changes, sleep problems.

The negative impact of PTH may be an important concern, as most PTH have the clinical characteristics of episodic M, and often the typical presentation of a CM, two forms that are well-known as disabling conditions.

22.5.3 Treatment of PTH [3, 29, 30]

There are no evidence-based guidelines for PTH, and it is unclear whether pharmacological treatments which are generally used in primary headaches are effective.

In PTH forms with migraine features, triptans may be the first choice in symptomatic treatment, and prophylaxis with standard anti-M compounds should be started; tricyclic agents may be indicated in TTH-like forms.

The treatment of PTH could be complicated by the presence of other postconcussive symptoms and by coexisting conditions.

A combination of pharmacological and non-pharmacological or local treatment (physiotherapy, occipital nerve blocks, relaxation training, stress management therapy, etc.) may be particularly effective.

22.5.3.1 Risk Factors for Chronification and Long-Term Prognosis [3, 29, 30]

Overall, the long-term prognosis is variable across different patients.

In most subjects, PTH gradually resolves in a period of some weeks/months. In a minority of patients, headache lasts for more than 1 year – up to several years – and becomes more disabling or refractory to treatments. The most relevant predictors to develop PTH are a previous history of primary headaches and a mild injury. Comorbid psychiatric disorders and female gender, as well as age $\leq$60 are reported as possible risk factors for PTH in some studies.

All the above-reported aspects are likely to contribute to a less favorable prognosis, namely

to PTH chronification. As discussed for M and TTH, the frequent use of drugs for the symptomatic treatment may also lead to the persistence of PTH, causing MO.

There are many prejudices against patients with PTH, and often the presence of litigation suggests malingering or overestimation of symptoms. The majority of available evidence indicates that headache characteristics are similar in patients with insurance claims and in those without medical–legal controversies, though the course of PTH may be more favorable after legal settlements in some patients.

Headache after mild traumatic brain injury is very common, and often persistent, at least during the first year after the traumatic event. Though no definitive evidence exists about the best treatment options in PTH patients, we suggest to consider early treatment – particularly when migraine features are evident – and appropriate therapy for the possible coexisting symptoms in the context of a postconcussive syndrome, to avoid chronification and relevant disability.

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Disorders of Cerebrospinal Fluid Circulation

23

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Abbreviations

COL5A1+2, Collagen 5A1+2; CSF, cerebrospinal fluid; ELD, external lumbar drain; EPB, epidural blood patch; HDTC, hereditary disorders of connective tissue; ICP, intracranial pressure; IIH, idiopathic intracranial hypertension; iNPH, idiopathic normal pressure hydrocephalus; LPS, lumboperitoneal shunt; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; ONSF, optic nerve sheath fenestration; PTCS, pseudotumor cerebri syndrome; SIH, spontaneous intracranial hypotension; TSS, stenotic transverse sinuses; VPS, ventricoloperitoneal shunt

Spontaneous intracranial hypotension (SIH) and idiopathic intracranial hypertension (IIH) are often underdiagnosed, rare disorders of uncertain pathogenesis. Idiopathic normal pressure hydrocephalus (iNPH) is a more frequent disease in which precise characteristics predict therapeutic response.

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23.1 Spontaneous Intracranial Hypotension (SIH)

Key Facts

- **Terminology** – SIH is a syndrome due to reduced intracranial CSF pressure and/or volume
- **Pathogenesis** – SIH is caused by spinal CSF leaks often of undetermined cause, or to congenital weakness of the dural sac, trivial trauma, spondylotic spurs, herniated discs
- **Diagnostic markers**
  - **Clinical features**
    - Orthostatic headache often aggravated by Valsalva maneuver
    - Nausea and vomiting
    - Diplopia (6th cranial nerve palsy)
    - Tinnitus, dizziness
    - Photophobia, visual blurring
  - **Genetics**
    - Abnormalities in COL5A1/2 in E-DII
    - Marfan's syndrome; other disorders of connective tissue
  - **Cerebrospinal fluid**
    - Low CSF opening pressure
    - Protein concentration and erythrocyte count may be high
    - Lymphocytic pleocytosis (up to 40 cells/mm^3), may be present
  - **Imaging**
    - Diffuse linear pachymeningeal enhancement
    - "Sagging" or "sinking" of the brain
    - Subdural fluid collections
    - Engorged cerebral venous sinuses
- **Top differential diagnoses**
  - Chiari I malformation
  - Meningeal carcinomatosis
  - Infective-inflammatory or granulomatous diseases
- **Prognosis**
  - *Therapy and prognosis*
    - Most patients obtain complete recovery by conservative management
    - Epidural blood patch (EBP) is quite often efficacious; surgery is reserved for refractory cases
    - Recurrence may occur
    - Rare patients remain symptomatic and work disabled

23.1.1 Terminology and Definitions

Spontaneous intracranial hypotension (SIH) is a syndrome due to reduced intracranial CSF pressure and/or volume.

23.1.2 Demographics

SIH is a relatively rare headache disorder with a female to male ratio of 2:1. Its annual incidence is 5/100,000 people, with a prevalence of 1/50,000 [1, 2]. The typical age of onset is 40–60 years, but children and the elderly may be affected.

23.1.3 Clinical Features and Diagnostic Criteria

SIH is syndrome is characterized by "orthostatic" headache beginning and worsening within 15 min in upright position, and improving in 15–30 min after lying down.

The headache is commonly holocranial and aggravated by Valsalva maneuver. A variety of other manifestations such as diplopia (often due to VI nerve palsy), nausea, dizziness, radicular upper limbs pain, neck stiffness, and, rarely, symptoms of hindbrain or even of diencephalon transforaminal herniation may occur. Altered state of consciousness (encephalopathy, lethargy, coma) and personality change may be associated in more severe cases.

Normal CSF pressure, normal cranial MRI, and even absence of postural headache have been reported.

The diagnostic criteria for SIH are as follows:

1. Orthostatic headache
2. Presence of at least one of the following: (a) low opening pressure (<60 mmH_2O), (b) sustained improvement of symptoms after epidural blood patching, (c) demonstration of an active spinal

CSF leak, and (d) cranial MRI changes of intracranial hypotension
3. No recent history of dural puncture
4. Not attributable to another disorder [3].

23.1.4 Pathophysiology

SIH is the result of a spontaneous CSF leak, often located in the spine, which leads to reduced CSF pressure and volume. Although the cause of CSF loss is rarely identified, two main factors have been claimed to play a role in the pathophysiology of SIH: trauma (even trivial) and fragile meninges. At least a third of SIH patients report intense coughing, weight lifting, sports, or other physical stress prior to headache onset, suggesting that a mechanical factor may produce dural sac fissures [4].

Some authors suggest that abnormalities observed in connective tissue disorders (e.g., in Marfan or in Ehlers-Danlos syndromes) may predispose to microlesions and hence to CSF leakage. Sinking of the brain and the resultant traction of its pain-sensitive suspending structures is the main cause of the orthostatic headache. Dilatation of cerebral veins and venous sinuses may also be a further and perhaps even the dominant mechanism in causing pain.

23.1.5 Diagnostic Markers

CSF Opening pressure is usually low, but within normal limits in one fourth of patients.

Pleocytosis, elevated erythrocytes number and protein concentration may appear.

Genetics Spontaneous CSF leaks are associated with a spectrum of hereditary disorders of connective tissue (HDTC) including Marfan and Ehlers-Danlos syndromes. Their prevalence is estimated in 16–18 % of the cases [5]. Gene sequences of fibrillin 1, collagen 5A1+2 (COL5A1+2), collagen 3A1 (COL3A1), and Folliculin C may be performed.

Imaging Brain MRI without and with contrast is the first choice examination. The most characteristic findings are (1) diffuse dural thickening and enhancement along cerebral convexities, falx, tentorium, and, often, clivus; (2) subdural fluid collections or hematomas; and (3) sagging brain with midbrain caudal displacement [4] (Fig. 23.1). Additional findings may include decreased size of the ventricles, pituitary enlargement, and engorgement of the dural venous sinuses. In rare cases, no meningeal abnormalities are seen [6].

Spinal studies are performed to determine the exact location of the CSF leak.

Spinal MRI demonstrates three characteristic findings: (1) epidural fluid collections, (2) collapse of the dural sac with engorgement of the epidural venous plexus, and (3) abnormalities of the root sleeves (Fig. 23.2). The epidural collections correspond to accumulations of CSF leaking into the epidural space [7]. Myelo-MR, radioisotope cisternography with Indium-111, and myelo-CT may reveal meningeal diverticula or Tarlov's cysts that often represent the site of the leak (Fig. 23.1).

23.1.6 Differential Diagnosis

The herniation of the cerebellar tonsils in SIH may simulate Chiari I malformation.

Meningeal dural enhancement may be confused with meningeal carcinomatosis.

At MRI, hypertrophic pachymeningitis may be indistinguishable from SIH.

Enlargement of the pituitary gland due to hyperemia may mimic pituitary tumors.

23.1.7 Treatment and Prognosis

Available treatment options are largely empiric; none have been evaluated in randomized, placebo-controlled clinical studies [4].

Initial therapy consists of strict bed rest supported by adequate oral hydration.

Spontaneous remissions within 2–6 months are observed in about 40 % of patients [8].

If further treatment is required, autologous lumbar epidural blood patch (EPB) is the first choice. With EPB, 61–75 % of patients (more than 90 % in the author's personal experience) improve.

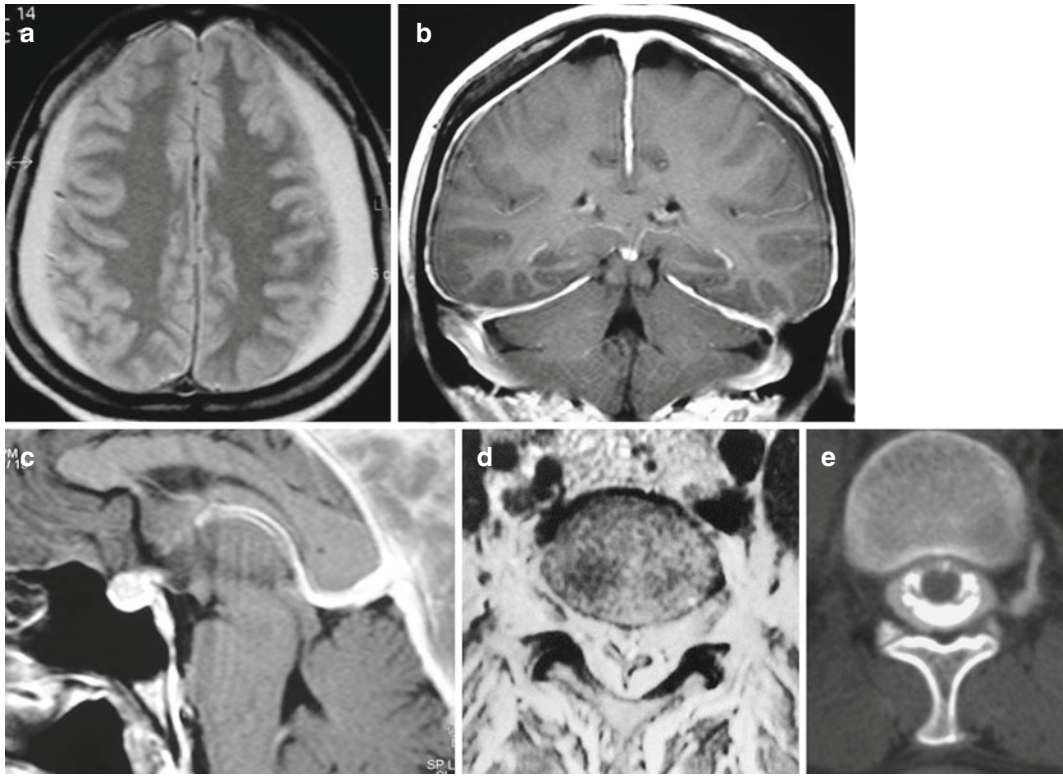

Fig. 23.1 SIH. Axial T2-weighted image and coronal T1-weighted image after contrast medium administration (**a**) and (**b**) demonstrated bilateral subdural fluid collections (*arrows*) and diffuse dural thickening and enhancement along both cerebral convexities, the falx and the tentorium. Sagittal T1-weighted image with contrast medium (**c**) shows sagging brain with midbrain caudal displacement and pituitary enlargement. Axial T1-weighted image with contrast medium at the level of L5 (**d**) demonstrates collapse of the dural sac with engorgement of the epidural venous plexus, and myelo-CT (**e**) shows CSF leaks (*arrowheads*)

Improvement may be obtained even months after the onset of pain [9].

Of 25 consecutive patients with spontaneous CSF leaks treated with EBP, nine patients (36 %) responded well to the first injection. Of 15 patients who received a second EBP, five became asymptomatic (33 %). Of eight patients who received three or more EBP (mean 4), four patients (50 %) showed symptoms remission. Bilateral chronic subdural hematoma caused by CSF leak had to be evacuated in two patients (5 %) [8].

In a large unpublished series (Enrico Ferrante, personal communication. E-mail: enricoferrante@libero.it), regarding 210 SIH patients (111 women and 99 men) submitted to blood patch and followed-up from 6 months to 8 years, 198 had a positive response, 10 patients were treated two or more times and only two did not achieve symptomatic remission.

Similar results were obtained in a group of 196 patients with SIH; 130 had a spontaneous recovery within 6 months. In 66 of the remaining cases, 58 recovered after one or more blood patches. In 4 cases, recovery was obtained only after surgery; in 4 patients SIH became chronic (author's personal experience).

The response to a single EBP may not be permanent, and complete relief of symptoms may only occur after two or more procedures.

Fibrin sealant may be considered as a second choice option.

Surgical intervention at the site of leak – if found – is safe and commonly successful in eliminating the cause of the leakage. In a minority of

patients (1–2 %), all therapeutic attempts fail; therefore, patients may suffer chronic symptoms and work disability.

Dementia and cognitive deficits are uncommon complications [1].

Although unusual, parkinsonism, ataxia, and/or stupor and coma have also been described.

23.2 Idiopathic Intracranial Hypertension (IIH)

Key Facts

- **Terminology** – IIH is a syndrome of increased intracranial pressure without identifiable cause and with normal CSF
  - *Clinical features*
    - Diffuse headache aggravated by physical activity and associated with nausea and vomiting.
    - Papilledema
- **Diagnostic markers**
  - **CSF**
    - Elevated opening pressure reaching more than 200 mmH_2O in nonobese and more than 250 mmH_2O in obese patients
  - **Imaging** – MRI is the study of choice, showing
    - Optic nerve distension
    - Empty sella with deformities of the pituitary gland; distension of the optic nerve sheath
    - Posterior globe flattening and tortuosity of the optic nerve
    - MRV shows venous narrowing or cerebral venous sinus thrombosis
- **Pathogenesis**
  - Causes are largely unknown
  - Obesity, delayed CSF absorption, and venous outflow abnormality are involved in the elevation of intracranial pressure
  - Stenotic transverse sinuses (TSS) have been observed in up to 90 % of IIH patients
- **Top differential diagnoses**
  - Migraine and tension-type headache
  - Optic disc swelling caused by different etiologies
  - Obstructive hydrocephalus
- **Prognosis**
  - IIH is a chronic disease that requires long-term treatment.
  - Permanent, mild, or moderate visual field constriction has been reported in the follow-up.
  - Prognosis is good in patients who are promptly diagnosed and receive appropriate treatment.
  - Recurrence is rare.

23.2.1 Terminology and Definitions

Idiopathic intracranial hypertension (IIH) (alias: pseudotumor cerebri, benign intracranial hypertension) is a syndrome of increased intracranial pressure with no identifiable cause and with normal CSF composition related to an altered cerebrospinal fluid (CSF) hydrodynamics.

23.2.2 Demographics

The annual incidence is 0.9 cases per 100,000 with a prevalence of 8.6 cases per 100,000. The disorder usually affects obese women of childbearing age. In adults, the female to male ratio ranges between 4.3 and 5.0:1.0 [2].

23.2.3 Clinical Features

The typical IIH patient is an overweight woman of short stature. Diffuse headache, aggravated by physical activity, often associated to nausea and vomiting, is the most common complain. Papilledema, typically present in IIH, may cause scotomas and from transient dimming of vision to complete visual loss. A protracted course, last-

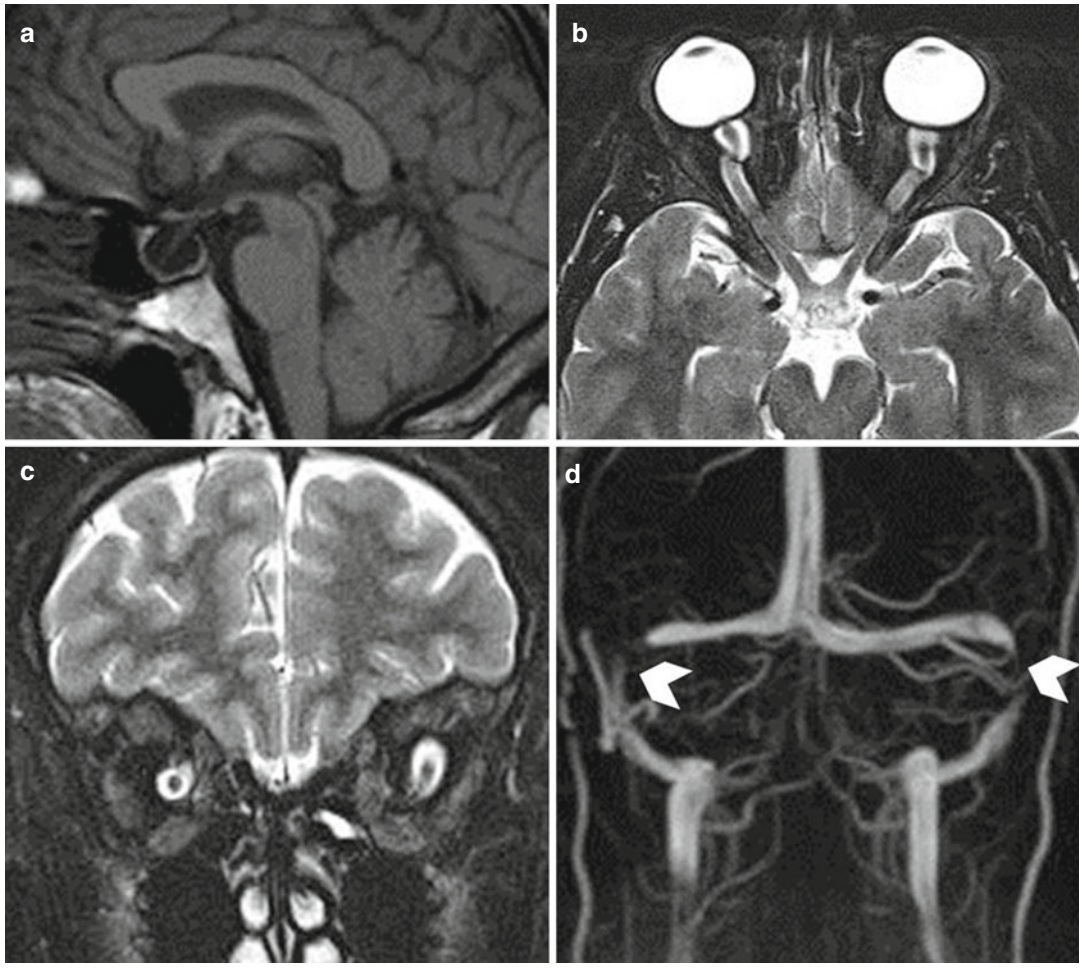

Fig. 23.2 IIH. Sagittal T1-weighted image (**a**) shows a huge empty sella. Nerve tortuosity, nerve sheath distention, and flattening of the globe and papilla in globe are demonstrated in axial and coronal T2-weighted images (**b**, **c**). In venous MR angiography stenosis, in the middle portion of bilateral transverse sinuses (*arrowheads*) is visible (**d**)

ing months to years, appears to be common; however, a subset of patients may show a more fulminant course with rapid development of vision loss within a few weeks from onset.

Definite diagnostic criteria for definite pseudotumor cerebri (PTCS) require: (1) papilledema, (2) normal neurologic examination except for cranial nerve abnormalities (usually unilateral or bilateral abducens nerve palsy), (3) normal brain parenchyma on MRI, (4) normal CSF composition, and (5) elevated lumbar puncture opening pressure (250 mm).

In the absence of papilledema, the diagnosis of PTCS can be made if the second and the fifth criteria described above are satisfied. In the absence of papilledema or sixth nerve palsy, a diagnosis of PTCS can be suggested, but not definitively made, if the second and the fifth above criteria are satisfied together with three of the following neuroradiological find-

ings: (1) empty sella, (2) flattening of the posterior aspect of the globe, and (3) distension of the perioptic subarachnoid space with or without tortuous optic nerve, transverse sinus stenosis. A diagnosis of PTCS is definite if the patient fulfils 1–5 criteria. The diagnosis is considered probable if 1–4 criteria are satisfied and the CSF open pressure is lower than specified [10].

23.2.4 Diagnostic Markers

CSF Elevated CSF opening pressure (more than 200 mmH_2O in nonobese patients; more than 250 mmH_2O in the obese) is normally found. Increases of intracranial pressure may occur intermittently. Their demonstration may require continuous monitoring in some patients.

MRI is the study of choice. Signs of elevated intracranial pressure: optic nerve tortuosity and distension, enlargement of its sheath, empty sella, and posterior eye globe flattening are frequently found. Magnetic resonance venography (MRV) may show venous narrowing or venous sinus thrombosis. Venous sinus occlusion and arteriovenous fistulas may produce PTCS [10, 11] (Fig. 23.2).

23.2.5 Pathogenesis

The underlying cause of IIH is largely unknown.

Obesity is present in more than 70 % of adult IIH patients. Body mass index correlates with CSF opening pressure so that weight reduction results in decreased intracranial pressure.

Stenotic transverse sinuses (TSS) have been observed in up to 90 % IIH patients, but there are controversies as to whether TSS cause or are the consequence of raised intracranial pressure.

Reduction of intracranial pressure through CSF subtraction (by lumbar puncture or diversion procedures) may improve IIH.

23.2.6 Differential Diagnosis

Papilledema may have a similar appearance to optic disc swelling of different causes.

Adhesions of arachnoid granulations from infection or subarachnoid hemorrhage may modify CSF reabsorption and cause elevated intracranial pressure (ICP).

Obstructive hydrocephalus should be considered in the differential diagnosis [12].

23.2.7 Treatment and Prognosis

IIH is a substantially chronic disease in which recurrences, sometimes correlated with recent weight gain, are unpredictable.

Many patients suffer visual impairment at diagnosis, and about 30 % of them do not achieve complete remission.

There are few prospective studies of the natural history of idiopathic intracranial hypertension, but protracted courses lasting months to years appear to be common. Relapses may occur in one fourth of cases and a subset of patients (usually obese women) may exhibit fulminant course causing vision loss within a few weeks from the onset.

Many factors play a negative role in prognosis of IIH: presence of visual deficit at onset, anemia, black race, and severe obesity among others. Drugs (tetracyclines, estrogens, growth hormone, and excess of vitamin A, etc.) are suspected to trigger or aggravate IIH.

Absence of papilledema probably predicts positive IIH course with lower risk of vision loss.

The principal aim of IIH treatment is the preservation of vision and headache relief; weight loss is crucial for the success of therapy because

it reduces intracranial pressure, papilledema, and headache [13].

Papilledema is a major risk factor, being the actual cause of poor vision and optic atrophy in up to one third of patients.

In an old study regarding 57 patients followed- up for 5–41 years, 24 % developed blindness or severe visual impairment [14].

Medical therapy Therapy usually obtains gradual improvement and/or stabilization, but not necessarily remission of symptoms. About 6–14 % of patients, to a maximum of 24 %, retain persistent elevated intracranial pressure, papilledema, and residual visual field deficits [14].

Drugs Carbonic anhydrase inhibitors, such as acetazolamide (2–4 g/day), and topiramate are effective in reducing intracranial pressure and improving IIH symptoms. However, evidence supporting its efficacy is mostly observational. Topiramate carries the additional benefit of inducing weight reduction.

Surgery Evacuative lumbar puncture improves IIH headache. It is still unclear why even a short-lasting reduction of CSF pressure may obtain persistent headache relief. If weight loss and pharmacological treatment fail, and visual loss is progressive, CSF diversion procedures such as a ventriculoperitoneal (VPS) or lumboperitoneal shunt (LPS) should be considered.

Visual outcomes from intracranial venous stent placement and cerebrospinal fluid diversion procedures are rarely reported.

As a rule, surgery results in a favorable outcome, but exceptions are described.

Of 16 patients, all of whom were obese women in which visual impairment occurred within 4 weeks from onset of IIH symptoms, 50 % remained almost blind and all had severely impaired vision even after repeat lumbar puncture (11 of the 16 patients), optic nerve sheath fenestration (5 cases), lumboperitoneal CSF shunting procedure (9 cases), and ventriculoperitoneal shunting procedure (two cases) [15].

In a review, 17 patients treated by stent placement, 31 by VPS shunt placement, 44 by LPS, and 252 patients by optic nerve sheath fenestration (ONSF) have been followed-up for a mean time of 11.8 months (patients treated with stents) to 57.2 months for LP shunts. Improvement or remission of vision deficit was obtained in 38.7 % of patients submitted to VP shunt placement, in 47 % after stent, in 44.6 % of patients after LP shunt, and in 80 % of eyes after ONSD [16]. However, at long-term follow-up regarding 75 eyes submitted to ONSF, 51 eyes (68 %) showed improvement (36 %) or stabilization (32 %) of visual function. Twenty-four (32 %) had deterioration of visual function after an initial success of decompression [17].

The most common complication of LPS is failure of the shunt, which occurs in 48–86 % of patients. Shunting remains an option for patients with negative response to other treatment approaches, but must be considered with caution in IIH.

Optic nerve sheath fenestration may be considered in patients with papilledema and visual disturbances as main symptoms.

Endovascular stenting Regardless of the cause of the stenosis, endovascular stenting improves CSF outflow, reduces venous pressure, and increases CSF absorption diminishing intracerebral pressure in patients with TSS. Of 143 patients treated with venous stenting, 88 % reported improvement of headache and 87 % had improved visual symptoms [18].

With treatment, there is usually gradual improvement and/or stabilization, but not necessarily recovery; many patients have persistent papilledema, elevated intracranial pressure, and residual visual field deficits that may worsen until blindness. The prognosis is better in early diagnosed and appropriately treated patients [2, 12].

23.3 Idiopathic Normal Pressure Hydrocephalus (iNPH)

Key Facts

- **Terminology** – Idiopathic normal pressure hydrocephalus (iNPH) is a syndrome characterized by impaired gait, mild cognitive impairment or dementia, urinary incontinence, and ventricular enlargement
- **Pathogenesis** – Disturbance of the cerebrospinal fluid (SF) circulation probably due to block of CSF flow between the basal cisterns and the arachnoid granulations
- **Diagnostic markers**
  - **Clinical features**
    - Impaired gait
    - Cognitive impairment
    - Urinary urgency/incontinence
    - **Imaging**
    - MRI is the study of choice
    - Enlarged ventricles
    - Disproportion between the enlarged Sylvian fissure/basal cisterns and the remaining subarachnoid spaces
    - High-resolution MRI identify/exclude aqueductal stenosis
    - MRI PC show the hyperdynamic aqueductal CSF flow
- **Top differential diagnoses**
  - Parkinsonism
  - Lewy body dementia
  - Corticobasal degeneration
  - Progressive supranuclear palsy
  - Multiple system atrophy
  - Vascular dementia
  - Vitamin B12 deficiency
  - Cervical myelopathy
- **Treatment and prognosis**
  - Prognostic test (ELD)
  - No medical treatments are effective in iNPH
  - Ventricular-peritoneal shunting remains the preferred treatment with an overall success rate of 30–96 %
  - At a mean follow-up of 18 ± 13 months, improvement was observed in 75 % of patients
  - Surgery complications comprise shunt malfunction, infections, intracranial hemorrhages, subdural hematomas, low-pressure headache, seizures, and death or permanent neurologic deficits

23.3.1 Terminology and Definitions

Idiopathic normal pressure hydrocephalus (iNPH) is a syndrome of the elderly characterized by: (1) impaired gait, (2) urinary dysfunction, and (3) cognitive impairment, due to disorder of the cerebrospinal fluid (CSF) circulation.

The MRI diagnosis of "Possible" iNPH includes the demonstration of one or more of the classical triad in middle aged and elderly patients, ventricular dilation, and closing of the CSF space at high convexity. Patients with "Probable" iNPH improve after CSF removal. "Definite" iNPH shows clinical improvement after CSF shunt operation. The CSF tap test is a major diagnostic measure because of its simplicity, low invasiveness, and high specificity [19].

23.3.2 Epidemiology

The incidence is two cases per 100,000 individuals. In subjects older than 65 years, the prevalence of iNPH is 0.41 %. Demented patients carry iNPH in 1.6–5.4 % of cases; differential diagnosis between iNPH and degenerative dementias is mandatory because iNPH represents one of the few treatable dementias [19].

23.3.3 Clinical Features

By definition, iNPH is idiopathic. However, anamnesis of patients often includes known risk factors for communicating hydrocephalus: meningitis, encephalitis, traumatic brain injury

(including concussion), subarachnoid hemorrhage, and brain radiation.

The onset of symptoms is generally insidious, and often occurs between the sixth and eighth decade with gait disorder and abnormal postural reflexes. Sphincter dysfunction (usually urinary incontinence) and dementia may follow.

Although any of the main iNPH symptoms may be the initial symptom, gait impairment is usually the first and worst symptom [19, 20].

23.3.4 Differential Diagnosis

Disorders that may display simultaneously all three symptoms of iNPH include Parkinson, vascular or degenerative parkinsonisms, and degenerative dementias. Disorders that may have only two symptoms of iNPH include cervical stenosis and myelopathy, lumbosacral stenosis, and peripheral neuropathy [20].

23.3.5 Diagnostic Markers

TAC and MRI demonstrate enlarged ventricles without macroscopic obstruction to CSF flow and with a disproportion between enlarged Sylvian fissure and basal cisterns and the others subarachnoid spaces of brain convexity ("tight high convexity") that suggest a block of CSF flow between the basal cisterns and the arachnoid granulations. Enlarged ventricles against the falx cerebri result in an acute callosal angle ($\leq 90°$) seen on coronal view. The Evans ratio (the ratio of the maximum width of the frontal horns to the maximum width of the inner table of the cranium on the same axial slice) with a threshold index ≥ 0.3 may be useful for the diagnosis. Periventricular signal changes not attributable to microvascular damages may be observed.

High-speed and high-resolution MRI techniques can better identify/exclude aqueductal stenosis, and MRI phase-contrast techniques show the hyperdynamic aqueductal CSF flow that has been associated with shunt-responsive iNPH [19, 20].

23.3.6 Treatment and Prognosis

Treatment of idiopathic normal pressure hydrocephalus (iNPH) is challenging. No medical therapy is efficacious and ventricular-peritoneal shunting remains the preferred treatment.

The external lumbar drain (ELD) test (via lumbar puncture or spinal catheter) is specifically prognostic. It predicts the responsiveness of iNPH patients to CSF drainage.

Improvement to CSF removal confirms the diagnosis of iNPH and indicates that shunt surgery should be performed; on the contrary, without a positive response to CFS subtraction, surgery should not be performed [20]. ELD test has specificity of 96 %.

The overall success rate of surgical treatment of NPH varied from 30 to 96 % [19].

Factors suggestive of a good outcome were early diagnosis, gait disturbance as the predominant preoperative complaint, and positive response to cerebrospinal fluid dynamic tests. Only one, or two, or all symptoms may improve after shunt surgery and gait is the most likely to make progress.

In the largest series with prolonged follow-up and outcome analysis [21], 62 % of patients took advantage from shunt placement, and 34 % of these experienced prolonged benefit up to 24 months after the procedure, while the remaining patients experienced short-term symptoms relief.

In a recent review [22], at a mean follow-up of 18 ± 13 months, 75 % of 132 patients showed improvement in at least one of the symptoms.

In most circumstances, absence of progress after shunting or worsening after initial improvement is due to shunt malfunction or concomitant diseases, surgery, or hospitalization. The most significant complications of surgery are shunt malfunction, infections, intracranial hemorrhages, subdural hematomas, low-pressure headache, seizures, and permanent neurologic deficits or death [21].

The morbidity and mortality of CSF shunting procedures are significant. The pooled shunt complications and malfunction, infections, and subdural hemorrhages were 38 %. Additional surgery was necessary in 22 % of cases. Permanent neurologic deficit or death reached 6 % [23].

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Epilepsy and Myoclonus

24

Giorgio Battaglia and Marina Casazza

Key Facts

- **Definitions** – Epilepsy is a chronic disorder characterized by the tendency for spontaneously recurrent, unprovoked seizures. Myoclonus is a sudden and jerky involuntary movement, synchronous on antagonist muscles: both epileptic and non-epileptic myoclonus are recognized
- **Demographics** – The prevalence of active epilepsy is around 7 per 1.000 individuals
- **Clinical features** – Seizures of different types, alone or variably associated with neurological and mental deficits, with progressive, possibly fatal, course in some specific syndromes
- **Pathogenesis** – Etiology of epilepsy may vary greatly; the common pathogenic step is the generation of paroxysmal electrical activity within a limited population of neurons for focal seizures, or rapidly engaging bilaterally distributed neuronal networks for generalized ones
- **Diagnostic markers**
  - **CSF** – Presence of viruses, bacteria, fungi, and parasites; of auto-antibodies to voltage-gated channels and receptors, depending on the different causes
  - **Genetics** – Gene mutations of ion channels, receptors, or proteins relevant in migration or governing neuronal excitability
  - **Imaging** – From normal MRI to a variety of lesions of different nature, mainly but not exclusively in the temporal lobe, with diverse epileptogenic potential
  - **Neurophysiology** – EEG: from normal to generalized or focal interictal epileptiform abnormalities; it may be diagnostic; ictal EEG from scalp or SEEG studies to reveal epileptogenic areas and site-of-onset of seizures; MEG can help reveal epileptic focus through analysis of interictal abnormalities
  - **Other in vivo tests** – PET scans to reveal epileptogenic areas
  - **Pathology and biochemistry on brain tissue** – Highly variable, depending on the different epilepsy types. From normal cerebral tissue with minimal reactive gliosis, increasing in the course of epilepsy, to specific focal cortical lesions with cellular (dendrites, axons, terminals, cell bodies) and molecular (synaptic input imbalance, receptor expression) changes, and neuronal loss
- **Therapy** – Medical, through AED therapy; surgical, through conventional resective or functional surgery; neuromodulatory, through vagal nerve or deep brain stimulation
- **Prognosis** – Highly variable, favorable in 70 % of cases; drug resistance in about 30 % of cases; temporal lobe surgery favorable in 70–80 % of cases; the clinical course may be progressive or even fatal in selected syndromes

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Abbreviations

AED, anti-epileptic drug; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ARX, aristaless-related homeobox gene; BDZ, benzodiazepine; BECT, benign epilepsy with centrotemporal spikes; CA1, *Cornu Ammonis*, *subfield 1*; CAE, childhood absence epilepsy; CBZ, carbamazepine; CLB, clobazam; CASPR2, contactin-associated protein-like2; CCM1, cerebral cavernous malformation gene 1; CCM2, cerebral cavernous malformation gene 2; CCM3, cerebral cavernous malformation gene 3; CDKL5, cyclin-dependent kinase-like 5 gene; CHRNA2, neuronal acetylcholine receptor subunit alpha-2; CHRNA4, neuronal acetylcholine receptor subunit alpha-4; CHRNB2, neuronal acetylcholine receptor subunit beta-2; CZP, clonazepam; DBS, deep brain stimulation; DCX, ouble-cortin gene; DEPDC5, DEP domain-containing protein 5 gene; DNET, dysembryoplastic neuroepithetial tumors; DRPLA, dentatorubropallidoluysian atrophy; DTI-FT, diffusion tensor imaging with fiber tracking; DZP, diazepam; EMA, eyelid myoclonia with absences; EPM1, progressive myoclonus epilepsy gene 1; EPM2A, progressive myoclonus epilepsy gene 2A; EPM2B, progressive myoclonus epilepsy gene 2B; ESES, epilepsy with continuous spike and waves during sleep or electrical status epilepticus during sleep; ESM, ethosuximide; FCD, focal cortical dysplasia; FDG-PET, fluorodeoxyglucose-positron emission tomography; FLN1, filamin 1 gene; FS^+, febrile seizures plus; GABA, gamma-aminobutyric acid; GABRA1, gamma-aminobutyric acid receptor subunit alpha 1; GABRG2, gamma-aminobutyric acid receptor subunit gamma 2; GABRD, gamma-aminobutyric acid receptor subunit delta; GAD, glutamic acid decarboylase; GVG, vigabatrin; ILAE, international league against epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; LCM, lacosamide; LICE, lega italiana contro l′epilessia; LGI1, leucine-rich glioma inactivated 1; LIS1, lissencephaly gene 1; LMT, lamotrigine; LVT, levetiracetam; MAGI2, membrane-associated guanylate kinase inverted 2 gene; MCD, malformation of cortical development; MDL, midazolam; MEG, magnetoencephalography; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; MTS, mesial temporal lobe sclerosis; NFLE, nocturnal frontal lobe epilepsy; NGPSE, national general practice study of epilepsy; NMDA, N-methyl-D-aspartic acid; OXC, oxcarbazepine; PCDH19, protocadherin 19 gene; PHT, phenytoin; PLCB1, phospholipase C beta 1 gene; PME, progressive myoclonic epilepsy; PNES, psychogenic non-epileptic seizures; PNH, periventricular nodular heterotopia; PNKP, polynucleotide kinase 3-prime phosphatase gene; PolG1, DNA polymerase subunit gamma gene; SCN1A, voltage-gated sodium channel, type I alpha subunit gene; SCN1B, voltage-gated sodium channel, type I beta subunit gene; SCN2A, voltage-gated sodium channel, type II alpha subunit gene; SCN9A, voltage-gated sodium channel, type IX alpha subunit gene; SE, status epilepticus; SEEG, stereo-EEG; SLC25A22, solute carrier family 25 (mitochondrial carrier: glutamate), member 22 gene; SMR, standardized mortality ratio; SPECT, single photon emission computerized tomography; SPTAN1, spectrin, alpha, non-erythrocytic 1 gene; STP, stiripentol; STXBP1, syntaxin binding protein 1 gene; SUDEP, sudden death in epilepsy; SW, sharp waves; TLE, temporal lobe epilepsy; t-VNS, transcutaneous-VNS; VNS, vagal nerve stimulation; yrs, Years; VPA, valproic acid; ZNS, zonisamide.

24.1 Introduction

About 10 % of people will present at least a single seizure during lifetime, and a third of them will eventually develop epilepsy. Since epilepsy is a chronic disease requiring long-standing treatment, the prognosis takes on great relevance. However, it is still a greatly debated issue for two main reasons: first, different epileptic syndromes, both in childhood as well as in adulthood, may have greatly different clinical outcomes; second, even in single individual cases with similar types of epilepsy, clinical outcome could be very different, and predictors of outcome can be difficult to establish.

This chapter will try to link specific prognosis to specific epilepsy syndromes, and to provide prognostic parameters that can be useful to clinicians to orient prognosis in their individual patients.

24.2 Terminology and Definitions

The ILAE definition of an epileptic seizure [1] is: "a transient occurrence of signs and/or symptoms due to abnormal, excessive, or synchronous neuronal activity of the brain." Epilepsy is a chronic disorder characterized by the tendency for spontaneously recurrent, unprovoked seizures.

Seizures can be focal if the electrical activation originates from a limited population of neurons and is restricted to neural networks localized and limited to one hemisphere, or generalized, when the electrical activation occurs and rapidly engages bilaterally distributed networks [2].

Quite a number of electro-clinical syndromes are recognized, and organized according to the age of onset (Table 24.1) [2].

In addition, the ILAE classification recognizes clinical entities not strictly considered syndromes but representing clinically distinctive constellations due to specific lesions or other causes. Examples include mesial temporal lobe epilepsy associated with hippocampal sclerosis, gelastic seizures of hypothalamic hamartoma, and Rasmussen epilepsy.

Further, structural/metabolic epilepsies are determined by specific lesions, such as malformations of cortical development, neurocutaneous syndromes, tumors, vascular abnormalities, trauma, and so on.

Finally, epilepsies of unknown causes are recognized, encompassing all epilepsies that in the past were termed "cryptogenic" (i.e., the majority of epilepsy with focal seizures of adulthood).

Table 24.1 Electro-clinical syndromes and other epilepsies

Electro-clinical syndromes arranged by age at onset[a]
Neonatal period
Benign familial neonatal epilepsy (BFNE)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome
Infancy
Epilepsy of infancy with migrating focal seizures
West syndrome
Myoclonic epilepsy in infancy (MEI)
Benign infantile epilepsy
Benign familial infantile epilepsy
Dravet syndrome
Myoclonic encephalopathy in non-progressive disorders
Childhood
Febrile seizures plus (FS^+) (can start in infancy)
Panayiotopoulos syndrome
Epilepsy with myoclonic atonic (previously astatic) seizures
Benign epilepsy with centrotemporal spikes (BECTS)
Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
Late onset childhood occipital epilepsy (Gastaut type)
Epilepsy with myoclonic absences
Lennox-Gastaut syndrome
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)[b]
Landau–Kleffner syndrome (LKS)
Childhood absence epilepsy (CAE)
Adolescence – Adult
Juvenile absence epilepsy (JAE)
Juvenile myoclonic epilepsy (JME)
Epilepsy with generalized tonic–clonic seizures alone
Progressive myoclonus epilepsies (PME)
Autosomal dominant epilepsy with auditory features (ADEAF)
Other familial temporal lobe epilepsies
Less specific age relationship

(continued)

Table 24.1 (continued)

Familial focal epilepsy with variable foci (childhood to adult)
Reflex epilepsies
Distinctive constellations
Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
Rasmussen syndrome
Gelastic seizures with hypothalamic hamartoma
Hemiconvulsion–hemiplegia–epilepsy
Epilepsies that do not fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)
Epilepsies attributed to and organized by structural-metabolic causes
Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
Neurocutaneous syndromes (tuberous sclerosis complex, Sturge–Weber, etc.)
Tumor
Infection
Trauma
Angioma
Perinatal insults
Stroke
Etc.
Epilepsies of unknown cause
Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
Benign neonatal seizures (BNS)
Febrile seizures (FS)

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[a]The arrangement of electro-clinical syndromes does not reflect etiology
[b]Sometime referred to as electrical status epilepticus during slow sleep (ESES)

24.3 Epidemiology

The annual incidence of newly diagnosed epilepsy is 44 per 100,000 person-year in the United States (Rochester, Minnesota) [3] and between 33 and 68 in Europe [4]. The prevalence of active epilepsy is between 4 and 10 per 1000, with a slight, rarely significant predominance in males [4]. Most studies show a predominance of focal (60–70 %) over generalized seizures. The risk for epilepsy is greater in the first years of life, declines thereafter, and increases again in later years: the highest prevalence for epilepsy (9.4 per 1000) is in people aged 85 years or more. The lifetime risk for epilepsy is about 5 %. The probability of experiencing at least one unprovoked epileptic seizure at some stage during 80 years of life is almost 1 in 15 people [4].

24.4 Clinical Features According to Classification

The electro-clinical epileptic syndromes are distinctive clinical entities made up of a complex of electro-clinical features, symptoms and signs, with a specific age of onset. Epileptic constellations, although not strictly considered syndromes, are clinical entities with distinctive features. Also for the structural/metabolic epilepsies, it is possible to link the clinical features and course to the specific underlying cause. By contrast, for the epilepsies of unknown cause, clinical features may greatly vary, and parameters dictating the clinical course and outcome are frequently difficult to establish. In the following, we will briefly delineate the clinical features of the more frequent pediatric or adult-onset epileptic forms.

24.4.1 Epileptic Encephalopathies in Newborns and Infants

Syndrome	Age at onset	Seizure type	Etiology	EEG	Neurological outcome	Epileptologic outcome
Ohtahara	1st month	polymorphic	congenital cortical malformations	Suppression burst	Death in 50 % of cases in the first year, severe psychomotor delay in the others	Intractable epilepsy. Possible evolution into West syndrome
West	4–8 months	spasms	congenital cortical malformations, tuberous sclerosis, perinatal hypoxic lesions, cryptogenic	Hypsarrythmia	Death in 5–20 %. Psychomotor regression, mental retardation	Refractory epilepsy in 95 % of cases. Possible evolution into Lennox- Gastaut syndrome.
Dravet syndrome (severe myoclonic epilepsy in infancy)	1st year of life	Clonic, myoclonic and partial seizures	Genetically determined mutation of the X-linked PCDH19 gene, Xq22 locus, or de novo mutation of the SCN1A gene	Rapid generalized spikes or polyspikes, photosensitivity, multifocal spikes and spike and waves.	Psychomotor regression with ataxia and myoclonus	Refractory epilepsy

24.4.2 Focal and Generalized Epileptic Syndromes of Childhood

Syndrome	Age at onset	Seizure type	Etiology	EEG	Neurological outcome	Epileptologic outcome
Lennox Gastaut	3–5 yrs	Tonic and atonic with falls, atypical absences	Congenital cortical malformations, tuberous sclerosis, perinatal hypoxic lesions, cryptogenic	Slow spike and waves, polyspikes	Severe mental retardation	Refractory epilepsy
FS$^+$	>6 yrs	Persistence of febrile seizures, plus afebrile generalized seizures, absences, myoclonic and focal seizures	Genetic with autosomal dominance with incomplete dominance	Not specific, with variable epileptiform abnormalities	Usually normal	Controlled seizures in most cases
BECT	7–10 yrs	Morpheic focal sensitive-motor with possible secondary generalization	idiopathic	Normal organization of wakefulness and sleep. Typical monomorphic central or centrotemporal SW, unilateral or bilateral, often asynchronous.	Normal neurological development	Spontaneous remission, even without treatment, in 2–4 years after onset
Panayiotopoulos syndrome	1–15 yrs	Autonomic signs and symptoms, frequent headache and vomiting. In 50 % of cases status epilepticus	Idiopathic	Normal organization of wakefulness and sleep. Typical SW localized most on the occipital regions.	Normal neurological development	Spontaneous remission, even without treatment, in adolescence or shortly after onset
Late-onset childhood occipital epilepsy, or Gastaut syndrome	8–11 yrs	Stereotypical visual auras, sometimes followed by loss of consciousness and motor phenomena	Probably genetic	Normal background, frequent occipital spikes, mainly occurring upon eye closure	Normal neurological development	Spontaneous remission in 2–7 years from onset in 50–80 % of cases. EEG abnormalities may persist

Syndrome	Age at onset	Seizure type	Etiology	EEG	Neurological outcome	Epileptologic outcome
NFLE	1–14 yrs	Clusters of brief nocturnal motor seizures with hyperkinetic or tonic manifestations	Genetic, in most cases related to mutations of genes encoding subunits of the neuronal nicotinic acetylcholine receptor (CHRNA4, CHRNA2, CHRNB2)	Normal background, frequently normal interictal EEG; frontal low-voltage ictal spikes	Normal psychomotor development and neurologic examination in most cases	Seizure severity vary within families; seizures usually persist through adult life
ESES	4.5–14 yrs	Focal motor, tonic, atonic, atypical absences	Cryptogenic, or associated with heterogenic brain lesions	Multifocal and diffuse spikes and SW, that are continuous during slow sleep, occupying more than 85 % of it. Absent during REM sleep.	Progressive complex and severe neurological impairment, mainly concerning language function, with mental impairment and psychiatric disturbances	Seizures can be rather easily controlled, ESES is much more difficult to suppress, depending on the neuropsychological and behavioral outcome
CAE	3–12 yrs	High frequency more than daily absences, with associated eyelid myoclonia, simple automatisms	Genetic	Bilaterally synchronous 3 Hz spike and waves and interictal ictal discharges	Normal development	Good outcome, usually with complete remission, in one third of cases generalized easily controlled seizures
Epilepsy with myoclonic absences	2–12 yrs	Absences with bilateral rhythmical clonic jerks correlated with epileptiform EEG discharges	Genetic	Bilaterally synchronous 3 Hz spike and waves with poligraphic recording of associated myoclonia	Developmental cognitive impairment may be observed	Rather good outcome, with rare evolution toward a secondary generalized epilepsy
Epilepsy with myoclonic-atonic seizures	7 months-5 yrs	Febrile and afebrile generalized seizures, followed by myoclonic-atonic seizures, determining falls, and absences	Probably genetic	Slowing of background activity, generalized irregular polyspikes and waves	Mild or even severe cognitive impairment or dementia might manifest	Rather good outcome, with tendency to relapse, mostly generalized tonic-clonic seizures

(continued)

(continued)

Syndrome	Age at onset	Seizure type	Etiology	EEG	Neurological outcome	Epileptologic outcome
EMA or Jeavons syndrome	2–5 yrs	Typical absences associated with rapid eyelid myoclonia and upward deviation of the eyes	Probably genetic	Normal background, typical marked photosensitivity	Normal development	Absence seizures tend to persist into adult life
Landau–Kleffner syndrome	5–7 yrs	Rare focal motor and generalized, present in 70 % of patients. Progressive aphasia and psychomotor disturbances	Cryptogenic, or associated with heterogenic brain lesions	Multifocal bilateral spikes and spike and waves, often prevalent on temporal and parieto-occipital regions, activated during sleep, when they become subcontinuous	Language recovery depends on the reeducation and the correction of EEG activity	Epilepsy has a good outcome

24.4.3 Genetic or Presumably Genetic Generalized Epilepsies of Adolescence

1. *Juvenile absence epilepsy* or *JAE* occurs around puberty with absence seizures similar but by far less frequent than those of CAE. The incidence and prevalence of JAE in the general population are not known. Age of onset is 10–12 years.

   Diagnostic markers – The EEG counterpart is a bilaterally synchronous 3–4 Hz spike and wave discharge. Generalized tonic–clonic seizures are associated in 83 % of cases, and myoclonic jerks, mainly at awakening, may be present.

   Prognosis – Response to treatment for absences is very good but outcome is less favorable: JAE patients, particularly if experiencing tonic–clonic seizures, might require lifetime treatment.
2. *Juvenile myoclonic epilepsy* or *JME* is the most common form of genetic generalized epilepsy, accounting for 5–10 % of all epilepsy cases. Age of onset is between 12 and 18 years.

   Diagnostic markers – Clinical features include (i) myoclonic seizures, single or repetitive myoclonic jerks without loss of contact involving primarily upper arms and mainly occurring upon awakening; (ii) generalized tonic–clonic seizures, usually occurring a few years after myoclonic seizures, mainly on awakening, sometimes preceded by repetitive myoclonic jerks; (iii) absence seizures, in about 35 % of patients. Sleep deprivation and fatigue can facilitate seizure occurrence. The interictal EEG is abnormal in almost all patients, particularly after sleep deprivation, with 4–6 Hz poly-spike and wave discharges, which could be also asymmetric. Recent neurophysiological studies suggested that discharges in JME might involve rather restricted cortical networks including different regions of the frontal and temporal lobes.
3. *Epilepsy with generalized tonic–clonic seizures alone* may occur between 6 and 20 years of age.

   Diagnostic markers – It is characterized mostly by generalized tonic–clonic seizures occurring shortly after awakening, easily precipitated by sleep deprivation. Similar to that observed in JME, absence and myoclonic seizures may be present. As for JME, similar interictal poly-spike and wave discharges characterize the EEG of patients. The frequency of occurrence of this syndrome is difficult to establish, possibly for the genetic overlap with CAE, JAE, and JME.
4. *Familial TLE*. A number of familial temporal lobe epilepsies have been described in the last 15 years, including familial mesial TLE [5].

   Diagnostic markers – They are characterized by onset in adolescence or adulthood, benign course with medication-responsive focal seizures, and complex, possibly polygenic, mode of inheritance. Autosomal dominant epilepsy with auditory features are characterized by auditory auras preceding focal and generalized seizures, and are related to mutations of the *LGI1* gene, encoding a protein associated to the voltage-gated potassium channel complex [6].

24.4.4 Progressive Myoclonic Epilepsies (PMEs)

PMEs are a heterogeneous group of progressive diseases characterized by (i) myoclonus, (ii) tonic–clonic seizures, and (iii) neurologic deterioration. Disease onset is in late childhood or adolescence.

Diagnostic markers – In all forms, myoclonus is usually precipitated by action and posture. Causative genes have been identified for most forms. Different clinical entities are known, including Unverricht–Lundborg and Lafora diseases (the most frequent forms, see below), type III Gaucher diseases, GM2-gangliosidosis, sialidosis, some mitochondrial disorders (such as MERRF and MELAS), DRPLA, and the vast families of ceroid lipofuscinosis.

Prognosis – Neurologic deterioration may differ greatly, from mild deficits to severe impairment and disability, in many cases progressing to death. Dementia is present in some of these disorders.

1. *Unverricht-Lundborg disease* is the mildest PME form.

   Diagnostic markers – In contrast to other PME, it is progressive only in adolescence. Jerks typically consist of action myoclonus triggered by voluntary movement, posture, and external stimulations. The causative disease gene is EPM1, causing massive down-regulation of cystatin B.

   EEG shows normal background activity and generalized spike-waves triggered by photic driving, posterior low-amplitude spikes, and photosensitivity. By adulthood, the clinical picture becomes stable, with severe myoclonus, controlled seizures, and nearly normal cognitive functions.

   Prognosis – The disease usually takes a long course, possibly with a normal life span.
2. *Lafora disease* (from the Spanish neurologist Gonzalo Rodriguez-Lafora, who first described the disease and the typical accumulation bodies in neurons) is genetically related to autosomal recessively inherited mutations in the EPM2A (encoding laforin, 45 %), or EPM2B (encoding malin ligase, 45 %), or a yet undiscovered gene (remaining 10 % of cases).

   Diagnostic markers – Difficulties in school, myoclonic jerks, generalized seizures and visual hallucinations are the first symptoms. EEG shows progressive slowing of background activity, posterior low-amplitude spikes, and photosensitivity, and diffuse spike and wave discharges in more advanced disease stages.

   Prognosis – Myoclonus and seizures gradually worsen and become intractable, associated with dementia. Death occurs in about 6–10 years after onset, mainly due to aspiration pneumonia during status epilepticus, but some patients present a less severe form with extended survival.

24.4.5 Epileptic Constellations

They are clinical entities characterized by distinctive lesions, not affecting a specific age, but presenting with rather repeatable clinical, radiologic, and epileptologic patterns.

(a) *Diagnostic markers* – Mesial temporal lobe epilepsy associated with MTS is characterized at MRI by volume reduction/atrophy and increased T2 signal of the hippocampus and parahippocampal area and, neuropathologically, by severe neuronal cell loss and gliosis of Cornu Ammonis, subfield 1 (CA1), and subiculum. It presents distinctive electroclinical features, it is frequently drug-resistant, and it frequently leads to epilepsy surgery.

   Prognosis – It is one of the most frequent medically refractory forms of human epilepsy, and the relation between MTS and drug resistance is further underscored by its presence in 50–90 % of patients operated for intractable mesial temporal lobe epilepsy [7].

(b) *Hypothalamic hamartomas* (or other hypothalamic lesions) are typically associated with gelastic seizures and a particular electro-clinical pattern. Surgery is the treatment of choice (hypothalamic disconnection, but see also below).

(c) *Rasmussen Syndrome*, or Rasmussen encephalitis, is a rare, inflammatory, possibly immunomediated chronic and progressive disease typically affecting one hemisphere [8].

   Diagnostic markers – Main symptoms are progressive neurological deficits, including cognitive and motor deterioration, and intractable seizures, often in the form of epilepsia partialis continua and recurring epileptic status.

   Prognosis – AED treatment, long-term immunotherapy and, above all, surgery (hemispherotomy, functional hemispherectomy) represent possible therapeutic options.

24.4.6 Structural/Metabolic Epilepsies

This group of epilepsies is much more heterogenous with respect to previous ones, encompassing various types of epilepsy symptomatic of

different diseases: we recognize malformations of cortical development, tuberous sclerosis, cerebral tumors, either of low or of high grade, cerebral arteriovenous malformations, cavernous angiomas, vascular lesions, such as hemorrhagic or ischemic brain lesions, and traumatic brain injuries. These underlying lesions have different intrinsic epileptogenic potential. Seizure semiology depends on the site of the epileptic focus (in general, close to but not necessarily corresponding to the lesion itself): for instance, frontal seizures with clinical frontal semiology and ictal frontal EEG pattern may be observed either in a frontal cavernous angioma, or in a frontal post-traumatic malacic lesion. Seizure semiology must guide in evaluating the lesion site, and in particular cases, the opportunity for presurgical studies.

(a) *Brain malformations* or MCDs are a class of clinical entities originating from disruptions of different nature of the normal process of brain ontogenesis during prenatal life. When severe or diffuse, they represent a fairly common cause of developmental delay particularly in pediatric patients; when more localized, they are a fairly common cause of epilepsy in adolescents and adults. From a practical or clinical standpoint, the more frequent forms are lissencephaly/band heterotopia, polymicrogyria (Fig. 24.1), focal cortical dysplasia (FCD) and periventricular nodular heterotopia (PNH, Fig. 24.2). FCDs, particularly Taylor's type FCD, are highly epileptogenic lesions, as also demonstrated by stereo-EEG (SEEG) recordings within the lesion, very frequently, but not always, associated with early-onset, drug-resistant severe epilepsy [9].

Resective surgery is the treatment of choice and is highly successful in the majority of cases, particularly in children. All PNH patients are affected by focal epilepsy, non-particularly severe but drug-resistant in the vast majority of cases. Some bilateral and symmetrical cases are genetically determined by *FLN1* gene mutations. Ictal EEG and Stereo-EEG recordings in PNH patients suggest that seizures are generated by abnormal anatomic circuitries including the heterotopic nodules and adjacent cortical areas [10].

(b) Although any tumor type can cause seizures, low-grade tumors are more frequently associated with epilepsy than high-grade tumors (e.g., high-grade astrocytomas) [11]. High-grade tumors presenting with seizures are usually smaller than high-grade tumors presenting with focal neurological deficits. Low-grade tumors, as gangliogliomas, or lesions with intermediate features between dysplasia and tumors, such as dysembryoplastic neuroepithetial tumors (DNET), present with seizures in almost 100 % of cases. Meningiomas have a much lower incidence of associated epilepsy, usually well controlled by AEDs (see Chap. 25).

(c) Among vascular malformations, cavernous angiomas have a high incidence of epilepsy, near 99 %, largely determined by slight blood leakage and the subsequent deposit of

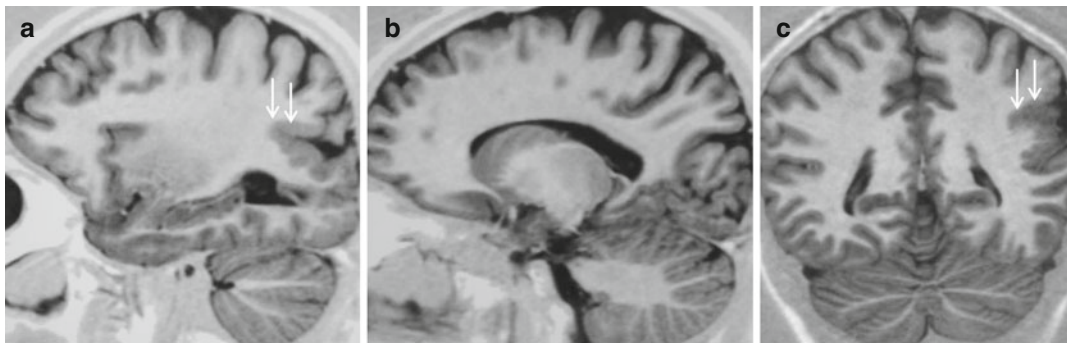

Fig. 24.1 Polimicrogyria. Sagittal and coronal IR images, **a–c**, demonstrate unilateral polimicrogyria involving the parietal and occipital regions (*arrows*): the cortical mantle is thickened, resulting from fusion of multiple adjacent small gyri. The gray-white matter interface is irregular due to fine interdigitation from abnormal convolutions

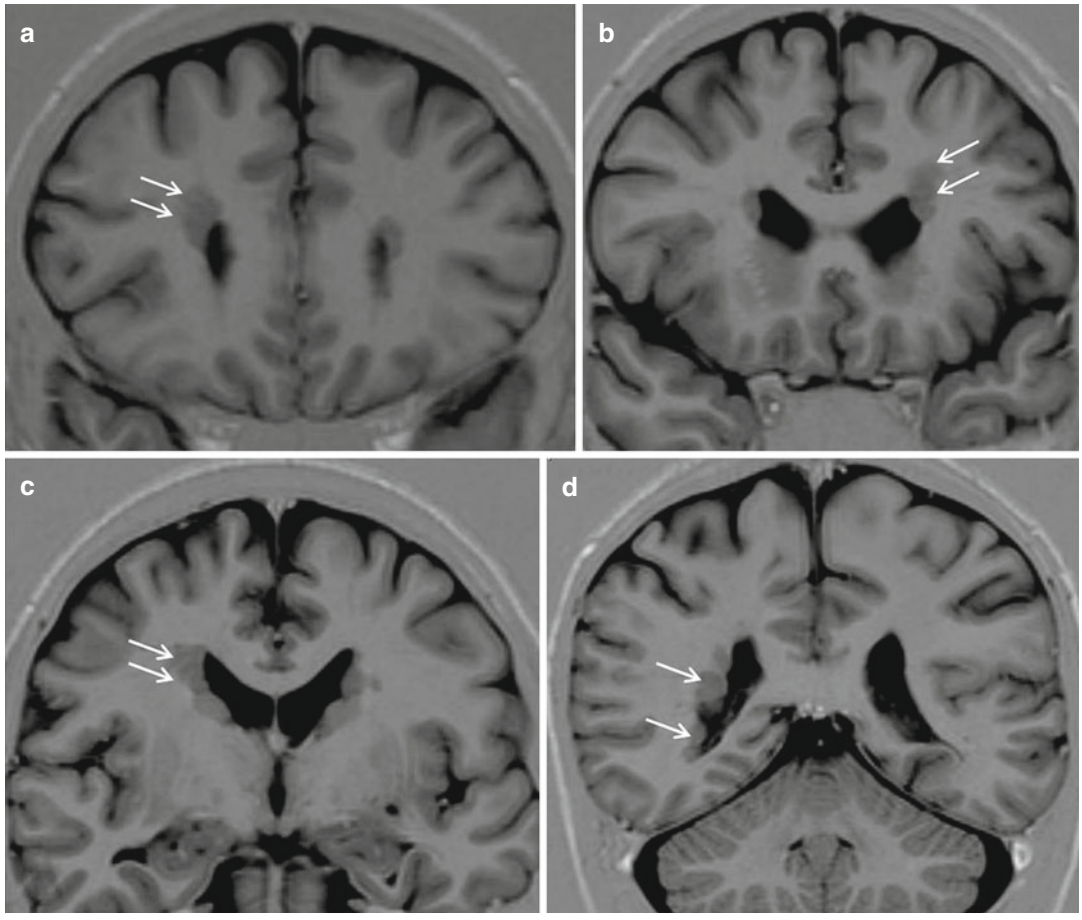

Fig. 24.2 Periventricular nodular heterotopia (PNH). Coronal IR images from anterior to posterior, **a**–**d**, show bilateral and asymmetrical multiple nodules lining the extension of the lateral walls of the lateral ventricles (*arrows*)

a hemosiderin ring. Familial cases have been described, linked to mutations of three different genes (*CCM1*, *CCM2*, and *CCM3*). Surgery can be curative in a large percentage of cases. However, multiple cavernous angiomas may be present in the same patient, and careful MRI analysis is mandatory.

24.4.7 Epilepsies of Unknown Causes

This is a large group of epilepsies, once termed "cryptogenic," in which a causative factor has not been found. As for the structural epilepsies (formerly called symptomatic), they can originate from the different cerebral lobes and, accordingly, when the seizure origin is sufficiently clear, they can be subdivided into frontal (mesial frontal, dorsolateral frontal, orbitofrontal and insular), temporal (neocortical and mesial), parietal, and occipital epilepsies. TLE is the most common form of adult focal epilepsy, and mesial (i.e., hippocampal) onset probably accounts for 80 % of all temporal lobe seizures [12]. Frontal lobe epilepsies are the second most common, accounting for approximately 20 % of cases. Parietal and occipital lobe epilepsies are less common, accounting for 6 % and 5–10 %, respectively, of localization-related epilepsies. The diagnostic course and treatment do not differ from those of localization-related symptomatic epilepsies.

24.5 Diagnostic Markers

For the intrinsic nature of seizures (sudden, repetitive phenomena, mostly occurring in otherwise healthy subjects), in most cases the diagnosis of epilepsy largely relies on the accurate evaluation of the clinical history of each individual patient.

Laboratory tests (serum and CSF) – In general, laboratory tests in epilepsy take on more relevance in the routine management of patients rather than in the diagnostic procedure. Indeed, routine blood and urine tests are mandatory to monitor possible side effects of the different AEDs on blood cell production, hepatic and renal function, and electrolyte balance. Regular blood sampling is also fundamental for monitoring basal of almost all AEDs (in the morning, before taking the first dose of the day). For a detailed analysis of the proper use of therapeutic drug monitoring see [13].

CSF analyses are obviously of pivotal importance in the diagnosis of systemic and CNS infections (e.g., viral, bacterial, fungal, and parasitic meningitis or meningo-encephalitis). More recently, it has been increasingly recognized that some epilepsy-related encephalitis can be antibody-mediated. Antibodies to voltage-gated potassium channels can provoke limbic encephalitis, characterized by focal seizures of temporal origin, amnesia, and unilateral or bilateral mesial temporal lobe inflammation possibly evolving into atrophy [14]. Antibodies to NMDA receptor subunits may provoke, predominantly in young women, a subacute-onset encephalopathy characterized by psychic symptoms, movement disorders, and focal seizures [15]. Other auto-antibodies possibly involved in the pathogenesis of focal epilepsy (particularly in temporal lobe epilepsy) include antibodies against two proteins associated to the voltage-gated potassium channel complex, CASPR2 and LGI1, anti-GABA receptors, GAD, and AMPA receptor subunits. When the patient clinical history is suggestive of an acute- or subacute-onset encephalopathy with seizures, these antibodies should be searched for in both CSF and serum.

Imaging – CT scan is of little help, except for recognizing calcifications in very restricted cases. MRI is mandatory, with contrast medium if a tumor or a lesion determing blood-brain-barrier disruption is suspected. MRI standardized protocols can now easily identify different epileptogenic lesions (e.g. MTS in the temporal lobes). However, it is always wise not to make an etiological diagnosis based on imaging only, since the finding of a brain lesion can be casual, and the epileptic focus can be localized at distance, or extend outside the boundaries of a lesion. Lesions can be judged as the cause of epilepsy if a good correlation exists with the electro-clinical data, i.e., semiologic ictal signs and symptoms, and interictal as well as ictal EEG. This notion is of particular relevance in the planning of a surgical strategy.

PET is another useful tool in detecting an area of reduced fluorodeoxyglucose uptake, usually related to the site of epileptic focus, even in presence of apparent structural normality. SPECT can give information on seizure focus, and can be employed in ictal (hyper-perfusion) and interictal (hypo-perfusion) conditions.

Genetics – Recently, a number of genes have been reported as causative for several epilepsy syndromes (mutations in the *ARX*, *CDKL5*, *SLC25A22*, and *STXBP1* genes in *Ohtahara syndrome*; *ARX*, *CDKL5*, *SLC25A22*, *SPTAN1*, *PLCb1*, *MAGI2*, and *PNKP* gene mutations in *West syndrome*. *SCN1B*, *SCN1A*, *SCN2A*, *SCN9a*, *GABRG2*, *GABRD* are genes mutated in families with *febrile seizures plus*; *SCN1A* and *PCDH19* gene mutation in *Dravet syndrome*; mutations of genes encoding subunits of the neuronal nicotinic acetylcholine receptor, CHRNA4, A2, and B2, in most cases of *autosomal dominant nocturnal frontal lobe epilepsy*; *LGI1* mutations in *autosomal dominant epilepsy with auditory features*). In addition, causative genes are known for most cases of progressive myoclonic epilepsies, such as mutations of *EPM1* for *Unverricht-Lundborg*,

EPM2A and *EPM2B* for *Lafora*, *PolG1* and mitochondrial DNA for *MERRF* and *MELAS*. Mutations have been found in some cases of malformations of cortical development such as of the *FLN1* gene for PNH, *DCX* and *LIS1* for lissencephaly/double cortex syndrome, different genes for various types of familial polymicrogyria, and the *DEPDC5* gene for familial patients with focal cortical dysplasia [16]. Mutations of the *CCM1*, *CCM2*, and *CCM3* genes have been found in familial but also sporadic cases of epileptogenic cavernous angiomas [17].

It is likely that a considerable degree of genetic overlap exists between *CAE*, *JAE*, *JME*, and *epilepsy with tonic–clonic seizures alone*. For *CAE* and *JAE*, a polygenic mode of transmission is the most likely mode of inheritance. Susceptibility to gene mutations in different ion channels or linkage for other genetic regions has been reported. For *JME*, different mutations can determine the same clinical phenotype. Both autosomal dominant (for the GABRA1 gene) and recessive inheritance have been reported in different families. As for CAE and JAE, the most likely mode of inheritance is polygenic transmission.

In pediatric focal epilepsies, the typical EEG trait of *BECT* could be dictated by an autosomal dominant pattern of inheritance. However, the combination of other genetic or even extrinsic influences may be relevant for the clinical expression of BECT (brain structural lesion have been also associated to BECT). A genetic predisposition is also likely for *Panayiotopoulos* and *Gastaut syndrome*, since a family history for epilepsy is present in 20–30 % of affected patients. In a severe and early-onset Panayiotopoulos patient, a mutation of the *SCN1A* gene was reported, whereas no linkage to specific chromosome regions has been demonstrated so far for Gastaut syndrome.

A more detailed update of genes relevant for the different epilepsy syndromes can be found at the LICE website, Genetic Commission, at www.lice.it.

Neurophysiology Interictal scalp EEG during wakefulness and sleep can provide relevant support to the clinical diagnosis of epileptic seizures. By no means does a normal EEG exclude a diagnosis of epilepsy. Ictal EEG scalp recordings are useful in confirming the diagnosis and in the differential diagnosis with non-epileptic phenomena. EEG monitoring is mandatory for epilepsy presurgical studies, in which the site of epileptic focus should be determined to decide opportunity and strategy of surgery.

A rather new neurophysiological method, magnetoencephalography or MEG offers interesting possibilities to be verified in the near future. MEG analyzes interictal EEG abnormalities, with much better spatial resolution than surface EEG, particularly when abnormal activity is generated in a cortical sulcus. MEG data can be projected on specific MRI images, thus providing relevant information on the location of the epileptic focus.

24.6 Special Situations

24.6.1 Febrile Seizures

They are generalized, age-related seizures, occurring during an acute febrile illness, in children aged from 6 months to 5–6 years. About 3 % of the population experiences febrile convulsions. They can occur in children with normal development, be simple and of short duration. Early (within the first year of life), repeated, lateralized, and prolonged febrile convulsions, and the existence of familiarity for epilepsy are all factors more likely associated with later epilepsy development (see below, prognosis).

24.6.2 The First Seizure

About 6 % of the population will experience a single afebrile seizure in life. In the case of provoked seizures (i.e., related to electrolyte imbalance, alcohol abuse or withdrawal, and precipitating medications), they are not diagnosed within the frame of epilepsy and AED treatment is not required.

Different is the case of single *unprovoked* seizures, whose recurrence rate ranges from 27 to

71 % [4]. A prospectively designed, community-based study of seizure recurrence gave an overall rate of seizure recurrence of 67 % within 1 year and 78 % within 3 years – NGPSE [18].

24.7 Prognosis

Several prognostic factors for recurrence have been identified (although not without controversy), including congenital neurological deficits, EEG epileptiform abnormalities, family history for epilepsy, and the presence of focal and nocturnal seizures, or mixed seizure types. However, the timing of treatment at the onset of epilepsy has no effect on long-term prognosis. Different studies demonstrated that even if patients treated after the first unprovoked seizure had a reduced risk of recurrence after 24 months compared with untreated patients, the probability of reaching 1 or 2 years remission was the same when therapy was started after the first or the second seizure [18].

24.7.1 Status Epilepticus (SE)

24.7.1.1 Definition

SE is defined as an epileptic activity continuing for 30 min or more or a series of epileptic seizures during which function is not regained between seizures for longer than 30 min.

Non-convulsive types of SE include:

(a) Absence SE and myoclonic SE, occurring in idiopathic generalized epilepsy of childhood and adolescence, but also rarely in adult or even elderly patients, as a result of drug withdrawal;
(b) Complex partial SE, more frequently occurring in adults; and
(c) Epilepsia partialis continua, characterized by repetitive focal motor seizures recurring every few seconds or minutes for very prolonged periods of time.

Convulsive or tonic–clonic SE is the more dangerous form, since it may evolve into refractory SE (when treatment with anesthetics is required), or super refractory SE (lasting more than 24 h under anesthesia or recurring when anesthetics are reduced or withdrawn), which are characterized by high mortality rates (see below).

24.7.1.2 Epidemiology

Incidence of SE ranges from 10 to 60 cases/10^5 per year, according to seven population-based studies of SE, peaking in the very young and the elderly [19]. The frequency of underlying major etiologies varies among published studies and show marked geographic differences. Major causes include febrile illnesses associated with systemic and CNS infections (particularly in children), acute cerebrovascular diseases (stroke is the more prevalent cause with increasing age), alcohol and drug abuse, and metabolic disorders. Brain tumors and trauma are less frequent cause of SE. In a sizeable proportion of cases (up to 15 % of patients), no evident cause is present (cryptogenic SE). In patients with a previous history of epilepsy, SE is frequently determined by low or absent antiepileptic drug levels [19].

24.7.1.3 Treatment

The *treatment* protocol for tonic–clonic SE, although not sufficiently supported by controlled study on efficacy and follow-up, is widely accepted and used in most tertiary care centers [20].

In the early phases of SE rectal, buccal, intranasal (if out-of-hospital), or intravenous – IV – (if facilities for resuscitation are available) benzodiazepines are first used, followed by IV AEDs (phenytoin, fosphenytoin, phenobarbital, valproic acid) and, if necessary, by the induction of anesthesia (midazolam, thiopental or phenobarbital, and propofol [21], also see below).

Although the lack of controlled studies hampers the evaluation of literature data, midazolam seems superior to propofol and barbiturates (thiopental or pentobarbital) in terms of reduced death rates during infusion, reduced breakthrough seizures (i.e., recurring after initial control and dictating switch of therapy) and withdrawal seizures (occurring after drug withdrawal) [20]. The use of propofol can be complicated, particularly in

patients co-medicated with steroid or cathecolamines or children with prolonged treatment, by the frequently fatal propofol infusion syndrome, leading to rhabdomyolysis, metabolic acidosis, and heart and renal failure. For details in the use of a variety of second-line treatments of SE, including AEDs, see [20].

24.7.1.4 Prognosis

The prognosis of SE is strongly related to the nature of the underlying etiology (see [19], for review). In most fatal SE cases, death is due to the underlying disease alone or in combination with other causes.

1. SE associated with alcohol or drug (cocaine) toxicity and abuse is associated with 20 % mortality rate.
2. SE-related metabolic disorders (electrolyte imbalance, hypoglycemia, and so on) frequently require mechanical ventilation and have a significant mortality rate (10–35 %).
3. Acute CNS infections and encephalitis, particularly frequent in children, are associated with significant mortality and morbidity, including a substantial risk of subsequent epilepsy.
4. Stroke-induced SE is consistently associated with higher mortality and morbidity rates compared with other causes. Patients developing refractory SE have a particularly poor prognosis with high mortality rates. In general, the presence of SE is a negative outcome predictor in stroke patients.
5. SE occurring after acute cerebral hypoxia, particularly in cases of myoclonic SE in coma, has an inevitably poor outcome, and is worse than any other condition, with mortality rates of 60–100 %.
6. SE associated with withdrawal or low AED levels in formerly epileptic patients has an overall favorable prognosis (even in the case of refractory SE), with mortality rates of about 10 %.
7. When the etiology remains unresolved (cryptogenic, up to 15 % of patients) the prognosis is variable, although mortality rates are generally low.

In the case of refractory or super-refractory SE, any anesthetic drug will control SE in all cases, provided that dosage is sufficiently high. However, frequently occurring side effects such as hypotension or cardio-respiratory depression could represent a serious limit to increase dosages to appropriate levels.

Regardless the underlying cause, the long-term outcome of refractory and super-refractory SE is poor, being associated with death in 35 % of cases, neurological or undefined deficits in other 30 %, and recovery to baseline in 35 % of patients only [20].

24.8 Mortality and Sudden Death in Epilepsy

The standardized mortality ratio (SMR) is higher in epileptic patients than in the general population, and greatest in patients with symptomatic epilepsy, severe neurological deficits, and uncontrolled epilepsy with frequent seizures (SMR = 3.0 in total epileptic patients, 1.6 in idiopathic epilepsy, 4.3 in symptomatic epilepsy) [21]. More frequent causes of death are accidents (drowning), aspiration, pneumonia, SE, suicide, and new CNS insults.

24.8.1 Sudden Death in Epilepsy (SUDEP)

24.8.1.1 Definition and Clinical Features

SUDEP is "the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death of a patient with epilepsy with or without evidence of a seizure, excluding documented status epilepticus, and in which post-mortem examination does not reveal a structural or toxicological cause of death" [22]. SUDEP probably accounts for 15 % of all epilepsy-related deaths. The most consistent risk factor is high frequency of generalized tonic–clonic seizures. No diagnostic test and no autoptic pathognomonic signs are known. Most SUDEPs occur during sleep, in patients with tonic–clonic sei-

zures, mostly found in prone position. The mechanism could be an association of cardiac and respiratory abnormalities, along with loss of consciousness, leading to hypoventilation, postictal hypercapnia, hypoxia, and consequent bradycardia, asystolia, and death [23].

24.9 Differential Diagnosis (Including Non-epileptic Motor Phenomena and Psychogenic Seizures)

Different kinds of transient "loss of consciousness" can be confused with epileptic seizures. In particular:

- *Syncope*: It can have different etiologies, it can be benign, or an expression of dangerous cardiac pathologies. It can mimic clonic or tonic–clonic seizures in its convulsive form. The accurate history of the patient, detailed description of the event, cardiologic tests, tilt test, and neurophysiologic recordings can lead to the correct diagnosis [24].
- *Psychogenic Non-Epileptic Seizures* (*PNES*): In almost 10 % of epileptic patients, they are associated with epileptic seizures. Their manifestations are very variable, often including motor phenomena without epileptic features. History, but particularly video-EEG recordings demonstrating the clinical features of PNES and the absence of EEG abnormalities allow altogether a correct diagnosis in most cases [25];
- *Parasomnias*: It can be difficult to recognize the correct nature of nocturnal episodes only from the report of patients and relatives. In these cases, video-EEG recordings during nocturnal sleep can allow distinguishing between nocturnal epilepsy and parasomnias.

24.10 Prognosis

In general terms, prognosis describes the fate and the long-term outcome of a specific clinical condition. In the case of epilepsy, prognosis has not been analyzed in sufficient detail in the available literature, the main reason being that epilepsy is not a single disease, but rather a group of diverse clinical entities with different etiologies, age of onset, and clinical courses. Such diversity implies that selected patient populations, subdivided in the different epileptic syndromes, constellations, or clinical entities must be followed-up for prolonged periods of time in order to ensure a reliable prognostic perspective. These studies are demanding, and not available for all epileptic entities.

In Western countries, it is also impossible to speak about natural epilepsy history, since patients are always subjected to therapy, aside from limited and specifically benign epileptic syndromes of childhood. Theoretically, natural epilepsy history can be inferred from epidemiology studies in developing countries, which, however, consider epilepsy as a whole, not subdivided in specific epileptic syndromes.

In this last part of prognosis of the chapter, we will first consider general principles of medical treatment, the issue of drug withdrawal, as well as surgery and other invasive treatments. We will then analyze prognosis in the different epileptic entities in the case of both medical and surgical treatment. Finally, we will consider the prognosis of neurologic and psychic disabilities in the epileptic patient.

24.10.1 Therapy

The goal of medical epilepsy treatment is to obtain seizure freedom without side effects. Therefore, as AEDs are symptomatic drugs that need to be taken by patients for prolonged periods of time or even for their lifetime, and as AED-related side effects might be present daily, managing and controlling side effects must have the same relevance as controlling seizures. In addition, particularly in children, preserving cognitive functions and quality of life is another target of no less relevance.

The *first step of treatment*, after a correct diagnosis has been established, is choosing the more

appropriate time to start AED therapy. In both children and adults, treatment should be started after two unprovoked seizures, as the risk or recurrence is much higher after a second than after the first seizure, over 70 % versus 46 % [26]. However, this rule must be tailored to the clinical history of the individual patients.

In childhood, it is advisable to consider not treating children with benign syndromes and early treating those with symptomatic (or probably symptomatic) epilepsies or epileptic encephalopathies.

In adults, the personal history of the individual patient is a relevant issue in the decision of initiating treatment. Factors such as patients' occupation, driving needs, severity and timing (during sleep or when awake) of the seizures, and vulnerability in case of seizure recurrence (possibly in elderly patients) must be all taken into account. Also, it might be advisable to distinguish between patients at low risk (with one seizure only), medium risk (2 or 3 seizures, or abnormal EEG, or neurological disorder), or high risk of recurrence (two of the mentioned features or the presence of more than 3 seizures). In any case, the ultimate decision whether to accept treatment belongs to the informed patient or parents, i.e., individuals who have been given proper information regarding the possible course of epilepsy, potential risks of repeated seizures (including SUDEP), and possible side effects of AEDs to be taken [26].

The *second step of treatment* is the choice of which particular AED to start with. Even if monotherapy is the gold standard for treatment, no randomized controlled trial supports a particular AED as initial monotherapy specific for children (see [27] for review), whereas levetiracetam (LVT) and controlled release carbamazepine (CBZ) showed virtually identical efficacy in adults with focal seizures [28]. In practical terms, valproic acid (VPA) can be recommended as the first choice for generalized and CBZ for focal-onset seizures, even if a study suggested, not without controversy, that lamotrigine (LMT) and possibly oxcarbazepine (OXC) might be better tolerated as initial monotherapy for children and adults with focal seizures [29]. Other relevant factors to be taken into account include:

(a) Consider the pharmacologic properties of each individual AED;
(b) Do not increase excessively daily dosages, as only 13–15 % of patients further benefit from increasing from average to maximal AED dosages;
(c) Regarding generic substitution of proprietary AEDs, consider for a given patient the continuous supply of a generic drug from the same manufacturer.

Regarding specific AEDs:

(d) VPA, particularly at doses above 600 mg per day, might not be the drug of choice for women of childbearing potential (unless the inefficacy of other AEDs has been already proven) for the high risk of major fetal malformations in case of pregnancy, and the possible negative effect on cognitive development of fetal exposure;
(e) CBZ is frequently discontinued in older patients for the presence of side effects, and the possible interactions with other drugs frequently taken by the elderly;
(f) LVT is not recommended in patients with psychiatric co-morbidities, for the incidence of psychiatric adverse events;
(g) In childhood, some specific AEDs are indicated for specific syndromes, such as stiripentol (STP) for Dravet syndrome, vigabatrin (GVG) and hormone therapy for infantile spasms, benzodiazepines (BDZs) and hormone therapy for Landau–Kleffner syndrome and epilepsy with continuous spike and waves during sleep.

The following tables (Tables 24.2 and 24.3) show the main features of the today-available AEDs. In particular, Table 24.2 [26] illustrates titration rates, maintenance dosages, and frequency of administration of the different AEDs in adults; and Table 24.3 [27] illustrates the recommended drug options according to the specific epileptic syndromes of childhood and adolescence.

The *third step in treatment* is the next course of action after failure of the initial monotherapy.

Table 24.2 Titration rates, maintenance dosages, and frequency of administration of the different AEDs in adults

	Suggested titration rate	Suggested initial target maintenance dose (mg per day)	Usual maintenance doses (mg per day)	Frequency of administration
Carbamazepine	Start with 100 or 200 mg per day and increase to target dose over 1–4 weeks	400–600[a]	400–1600	2–3 times daily (twice daily with sustained-release formulations)
Clobazam	Start with 10 mg per day; if indicated, increase to 20 mg per day after 1–2 weeks	10	10–40	Once or twice daily
Eslicarbazepine acetate	Start with 400 mg per day and increase to target dose after 1–2 weeks	800	800–1200	Once daily
Ethosuximide	Start with 250 mg per day and increase to target dose over 1–3 weeks	500–750[a]	500–1500	2–3 times daily
Felbamate	Start with 600 or 1200 mg per day and increase to target dose over 10–21 days	1800–2400	1800–3600	3–4 times daily
Gabapentin	Start with 300–900 mg per day and increase to target dose over 5–10 days	900–1800	900–3600	2–3 times daily
Lacosamide	Start with 100 mg per day and increase by 100 mg after 1–2 weeks; if indicated, increase further by 100 mg after 1–2 weeks	200–300	200–400	Twice daily
Lamotrigine monotherapy (and comedication with enzyme inducers associated with valproate)	Start with 25 mg per day for 2 weeks, then increase to 50 mg per day for 2 weeks; further increases by 50 mg per day every 1–2 weeks	100–150[a]	100–300	Twice daily (once daily possible)
Lamotrigine and enzyme-inducing comedication (without valproate)	Start with 25 or 50 mg per day for 2 weeks, then increase to 50 or 100 mg per day for 2 weeks; further increases by 50–100 mg per day every 1–2 weeks	200–300	200–500	Twice daily
Lamotrigine and valproate comedication (without enzyme inducers)	Start with 25 mg on alternate days for 2 weeks, then 25 mg per day for 2 weeks; further increases by 25–50 mg per day every 1–2 weeks	100	100–200	Twice daily (once daily possible)

(continued)

Table 24.2 (continued)

	Suggested titration rate	Suggested initial target maintenance dose (mg per day)	Usual maintenance doses (mg per day)	Frequency of administration
Levetiracetam	Start with 500 or 1000 mg per day and increase if indicated after 2 weeks	1000[a]	1000–3000	Twice daily
Oxcarbazepine	Start with 300 mg per day and increase to target dose over 1–3 weeks	600–900[a]	600–2400	2–3 times daily
Phenobarbital	Start with 30–50 mg at bedtime and increase, if indicated, after 10–15 days	50–100[a]	50–200	Once daily
Phenytoin	Start with 100 mg per day and increase to target dose over 3–7 days	200–300[a]	200–400	Once or twice daily
Pregabalin	Start with 50–75 mg per day and increase to 150 mg over 2–4 weeks; further increases, if indicated, by increments of 75–150 mg every 2 weeks	150–300	150–600	2–3 times daily
Primidone	Start with 62.5 mg per day and increase to target dose over about 3 weeks; in patients on enzyme-inducing comedication, faster titration can be used	500–750[a]	500–1500	2–3 times daily
Rufinamide	Start with 200–400 mg per day and increase by 200–400 mg per day after 2 weeks; further increases, if indicated, by 400 mg per day every 2 weeks	400–1800	400–3200	Twice daily
Tiagabine	Start with 5 mg per day and increase by 5 mg increments at weekly intervals	30 (patients on enzyme inducers); 15 (patients not on enzyme inducers)	30–50 (patients on enzyme inducers); 15–30 (patients not on enzyme inducers)	2–4 times daily
Topiramate	Start with 25 mg per day and increase by 25 or 50 mg increments every 2 weeks	100[a]	100–400	Twice daily
Valproate	Start with 500 mg per day and increase, if indicated, after about 1 week	500–1000[a]	500–2500	Twice daily (once daily might be sometimes feasible, especially with sustained-release formulations)

Table 24.2 (continued)

	Suggested titration rate	Suggested initial target maintenance dose (mg per day)	Usual maintenance doses (mg per day)	Frequency of administration
Vigabatrin	Start with 250 or 500 mg per day and increase to target dose over 1–2 weeks	1000	1000–3000	Once or twice daily
Zonisamide	Start with 50 mg per day and increase to 100 mg per day after 1 week; further increases by 50 mg per day every 1–2 weeks or by 100 mg per day after 2 weeks	200	200–600	Twice daily

Modified from Perucca and Tomson [26] and reproduced from *Lancet Neurol* copyright 2011, Table 4, page 452 with permission of Wolters Kluwer

This information reflects the authors' experience and might differ from that reported in product information sheets. Different titration and dosing schemes might be indicated in relation to the clinical context and individual patient characteristics

[a]Suggested target dose for initial monotherapy in adults with newly diagnosed epilepsy; larger doses might be appropriate for patients with pharmacoresistant epilepsy

After reconsidering the pertinence of the initial diagnosis (about 20 % of AED treated UK patients were reported to have their diagnosis questioned after specialistic re-evaluation) and the possibility of non-compliance (see also below), the conventional recommendation is to switch gradually to monotherapy with another AED. However, combination therapy might also be considered, particularly in the case of severe epilepsy, when the first AED was partially effective, or in specific epileptic syndromes of childhood. Indeed, polytherapy is preferable to monotherapy in myoclonic-astatic epilepsy or in epilepsy with myoclonic absences, and some drugs may have synergistic effects, such as VPA and ethosuximide (ESM) for absence seizures and VPA and lamotrigine (LMT) for absence and myoclonic seizures. In the case of seizure clusters, or severe tonic–clonic seizures, the use of on-off benzodiazepines may be advisable (intrarectal diazepam, DZP; oral midazolam, MDL; or clobazam, CLB).

After failure of second monotherapy, the diagnosis of drug-resistant epilepsy may be made, and the possibility of epilepsy surgery might be considered. This is particularly advisable in the case of severe epilepsy syndromes or constellations in which clinical histories suggest medical intractability (e.g., Rasmussen encephalitis, symptomatic epilepsies related to FCD or MTS). However, the diagnosis of drug-resistant epilepsy should not be considered as synonymous of medical intractability, as recent evidence from retrospective studies suggested that changes in AED treatment could result in seizure remission in up to 28 % of patients with refractory epilepsy [30].

In the case of polytherapy, a number of important issues should be taken into consideration:

(a) Prevent over-treatment, mostly due to failure in reducing unsuccessful polytherapy;
(b) Pay attention to adverse effects, both dose-dependent neurotoxic effects and idiosyncratic reactions (e.g., Steven-Johnson syndromes, LMT-induced skin rashes, and VPA-induced severe hepatotoxicity, particularly in children);
(c) Consider the possibility of AED-induced aggravation of seizures (e.g., CBZ, phenytoin (PHT), and vigabatrin (GVG) may worsen absence and myoclonic seizures, LMT may aggravate epilepsy course in Dravet syndrome);
(d) Do not pursue seizure freedom at all costs, but address co-morbidities;

Table 24.3 Recommended drug options according to different epileptic syndromes of childhood and adolescence

	First-line drugs	Second-line drugs	Other drugs	Drugs to avoid (might worsen seizures)
Childhood absence Epilepsy	Ethosuximide Lamotrigine Valproate	Levetiracetam Topiramate		Carbamazepine Oxcarbazepine Phenytoin Tiagabine Vigabatrin
Juvenile absence Epilepsy	Lamotrigine Valproate	Levetiracetam Topiramate		Carbamazepine Oxcarbazepine Phenytoin Tiagabine Vigabatrin
Juvenile myoclonic Epilepsy	Lamotrigine Valproate	Clobazam Clonazepam Levetiracetam Topiramate	Acetazolamide	Carbamazepine Oxcarbazepine Phenytoin Tiagabine Vigabatrin
Epilepsy with generalized tonic–clonic seizures	Carbamazepine Lamotrigine Topiramate Valproate	Levetiracetam	Acetazolamide Clobazam Clonazepam Oxcarbazepine Phenobarbital Phenytoin Primidone	Tiagabine Vigabatrin
Focal epilepsies: cryptogenic or symptomatic	Carbamazepine Lamotrigine Oxcarbazepine Valproate Topiramate	Clobazam Gabapentin Levetiracetam Phenytoin Tiagabine	Acetazolamide Clonazepam Phenobarbital Primidone	
Infantile spasms	Hormone therapy[a] Vigabatrin	Clobazam Clonazepam Valproate Topiramate	Nitrazepam	Carbamazepine Oxcarbazepine
Benign epilepsy with centrotemporal spikes	Carbamazepine Lamotrigine Oxcarbazepine Valproate	Levetiracetam Topiramate	Sulthiame	
Benign epilepsy with occipital paroxysms	Carbamazepine Lamotrigine Oxcarbazepine Valproate	Levetiracetam Topiramate		
Dravet syndrome (severe myoclonic epilepsy of infancy)	Clobazam Clonazepam Valproate Topiramate	Levetiracetam Stiripentol	Phenobarbital	Carbamazepine Lamotrigine Oxcarbazepine Vigabatrin
Continuous spike wave of slow sleep	Clobazam Clonazepam Ethosuximide Hormone therapy[a] Lamotrigine Valproate	Levetiracetam Topiramate		Carbamazepine Oxcarbazepine Vigabatrin

Table 24.3 (continued)

	First-line drugs	Second-line drugs	Other drugs	Drugs to avoid (might worsen seizures)
Lennox-Gastaut syndrome	Lamotrigine Valproate Topiramate	Clobazam Clonazepam Ethosuximide Levetiracetam	Felbamate	Carbamazepine Oxcarbazepine
Landau–Kleffner syndrome	Hormone therapy[a] Lamotrigine Valproate	Levetiracetam Topiramate	Sulthiame	Carbamazepine Oxcarbazepine
Myoclonic astatic epilepsy	Clobazam Clonazepam Valproate Topiramate	Lamotrigine Levetiracetam		Carbamazepine Oxcarbazepine

Table reproduced from Raspall-Chaure et al. [27] *Lancet Neurol* copyright 2008 Table 3, page 61, with permission
[a]Hormone therapy (e.g., corticosteroids or adrenocorticotrophic hormone)

(e) Consider mechanisms of action of the different AEDs: combination of two sodium-channel blockers seems to offer poor additional benefit, whereas combinations of BDZ (e.g., CLB) and sodium-channel-blocking AEDs, LMT, and VPA, and lacosamide (LCM) with non-sodium-channel blockers might offer increased benefit in some patients.

Finally, in the opinion of the authors, three fundamental parameters – i.e., a precise seizure notebook and description, as well as the judicious use of serial EEG recordings and AED plasma-level monitoring – should always be considered not only for establishing the best therapy but also forecasting clinical course in each single individual patient.

24.10.2 AED Withdrawal

The *final step in treatment* is to offer AED discontinuation to seizure-free patients. After evaluating the actual situation of seizure-freedom – including seizures merely subjective or with minimal clinical expression – for a period of at least 2–4 years, it is wise not only to check the patient's attitude but also to consider the possible impact of seizure recurrence on the patient lifestyle and emotional/psychic status.

Patients should also be properly informed that re-instatement of AED treatment does not grant a return to seizure control, particularly when long time periods and many therapeutic regimens are required to completely dominate the seizures. AED withdrawal should be also considered very cautiously in particular epilepsy syndromes, such as JME, in which pre-existing data in the literature predict very high risk of recurrence (up to 90 %). Even if the pre-existing literature suggests a 6-month time-period for complete withdrawal, it is advisable to be more cautious and withdraw therapy in longer time periods. Even if there is no reported evidence of better outcome in case of very slow AED tapering, this "patient" strategy should provide useful information as to the minimal effective therapy for a given patient, allowing the use of serial, temporally spaced EEG tracings during withdrawal, i.e., the only available predictive parameter for prognostic purposes.

24.10.3 Epilepsy Surgery and Other Forms of Non-pharmacologic Treatment

In almost one third of cases, patients with focal epilepsy present refractory seizures, opening the possibility of epilepsy surgery. Before proposing or exploring the possibility of surgery, a careful evaluation of the risk/benefit ratio should be performed, taking into consideration type and frequency of seizures, and their negative impact on the patient's everyday life. In addition, seizures must be monomorphic (i.e., single-type seizures),

therefore suggesting a unique and localized neural network giving origin to seizures. The main goal in the proper surgery planning is identifying the epileptic focus (not necessarily the cerebral lesion) to surgically remove the functional circuitry fostering seizures. To achieve this goal, an accurate presurgical study is mandatory:

(a) Collect epilepsy history with precise description of seizure symptoms and signs and their temporal evolution;
(b) Ictal scalp video-EEG recordings during wakefulness and sleep are mandatory. Seizures must be recorded to verify whether they take origin from a unique cortical area, the removal of which would not determine functional deficits. In some cases adjunctive electrodes, such as sphenoidal or foramen ovale electrodes can be added to better explore the temporal regions. If scalp EEG recordings do not provide sufficient information, SEEG studies with depth electrodes must be performed to better define the site of seizure onset and the diffusion to adjacent areas;
(c) MRI must be performed and should be sufficiently detailed, without and with contrast medium, to show the possible presence of cortical/subcortical lesions, their extension and type;
(d) Functional MRI gives further information on the localization of language and motor areas, and the proximity/relationship with the epileptogenic area and/or cortical lesions;
(e) f-18 FDG PET can add information on epileptic focus site, often appearing as a reduced captation area;
(f) Neuropsychological tests can be of value in localizing mnesic, phasic, attentional and other deficits, linked with the epileptic focus. When the epileptogenic area is clearly identified, unique, and resectable without further deficits, surgery planning can be developed. Surgery in most cases involves resection of mesial temporal structures and the temporal pole. However, to increase the possibility of a good outcome, every surgery should be tailored to the single individual patient. Surgery can be performed also on frontal, parietal, and occipital lobes, even if stereo-EEG recordings are needed in higher percentages of cases. In general, best results are obtained after temporal lobe surgery.

In addition to traditional epilepsy surgery (tailored lobectomy or cortectomy), there are various other surgical possibilities, including:

(a) *Hemispherotomy/hemispherectomy*, consisting in the partial removal or complete removal/disconnection of one hemisphere, affected by a large lesion (dysplastic or congenital, either malacic or post-hemorrhagic or post-traumatic), with associated diffuse hemispheric malfunctioning, hemiplegia, and severe unilateral but frequently multifocal epilepsy. Severe epilepsy associated with Rasmussen encephalitis can be treated with this technique. Results of hemispherectomy are satisfactory, above all in vascular perinatal lesions, often with complete seizure control and no adjunctive neurological deficits (see below).
(b) *Corpus callosotomy* is the partial or complete section of corpus callosum, usually performed in epilepsies dominated by tonic or atonic falls, as in Lennox-Gastaut syndrome. Falling seizures can be reduced from 50 to 80 %, while results on other associated seizures are much less significant [31].
(c) *Neuromodulation*: since the early 1980s a number of drug-resistant focal epilepsies have been treated by vagal nerve stimulation (VNS), employing a subcutaneous device with electrodes fixed around the left vagus nerve. Up to 50–60 % of patients might experience satisfactory results from this kind of stimulation, but no predictive factors for good outcome have been identified so far. Transcutaneous vagal nerve stimulation (t-VNS), a more recently developed type of VNS, is based on the external stimulation of the left auricular nerve, a branch of the vagus nerve. The external stimulator acts transcutaneously and does not involve any surgical – permanent – procedure and thus is easy to use. Its outcome is similar to that of implanted VNS, but its results are, however, very preliminary.

(d) *Deep brain stimulation* (*DBS*) is another modulation technique, based on electrophysiologic devices stimulating different thalamic nuclei through implanted electrodes. The only large, internationally approved experience is DBS of the anterior thalamus, with seizure reduction of about 50 % in drug-resistant focal epilepsy patients (see below).

24.10.4 *Prognosis* after Medical Treatment

As indicated above (see *Clinical features*), epilepsy is neither a homogeneous clinical entity nor a single disease. Hence, from a prognostic standpoint, it is most important to recognize the different epileptic syndromes, because they have different clinical outcomes and response to therapy. It is equally necessary to differentiate the epileptic "constellations," since each of them is usually characterized by a similar clinical course and prognosis. Prognosis is far more difficult to establish in focal epilepsies of adulthood, either related to structural lesions or of unknown cause, since precise parameters for predicting clinical outcome at the disease onset are not available. In other words, it is more the clinical course of the single individual patient that may dictate the final outcome rather than the precise diagnosis/classification at the onset.

Febrile seizures: The NGPSE addressed the long-term prognosis of febrile seizures [32]. About 6 % of 220 children with FS developed subsequent epilepsy, i.e., a 10-fold increase in the risk of epilepsy than in the general population. About 10 % of children with FS developed neurological sequelae. As risk predictors, the more FS, the more likely was subsequent epilepsy, but no specific association between complex FS and subsequent epilepsy was found. Other studies, however, demonstrated higher rate of epilepsy in those children with complex FS (see [18], for review).

Epileptic syndromes: As already indicated, some epileptic syndromes of infancy, childhood, and adolescence are rather homogeneous in terms of clinical course, response to therapy, and outcome. Some of them – for instance Ohtahara, West (particularly if symptomatic), Dravet, and Lennox-Gastaut syndromes – run an unfavorable course in most cases, and are characterized by intractable seizures. In these cases, the main goal of clinical management is to stem seizures, avoid possibly precipitating AEDs, and address co-morbidities, while taking into particular account both psychic situations and cognitive functions.

The same applies to progressive myoclonic epilepsies, particularly in the less severe, non-fatal forms, in which proper control of myoclonic jerks and adequate supportive care may greatly help patients deal with their everyday life.

At the opposite end of the spectrum, quite a number of epileptic syndromes of childhood show a benign course, and, again, the right epilepsy diagnosis is the core of the medical management, correctly orienting the decision of not starting any kind of antiepileptic treatment and simply re-assuring little patients and parents of the favorable outcome (BECT, Panayiotopoulos and Gastaut syndrome, for instance).

By contrast, in some other syndromes, such as epilepsy with continuous spike and waves during sleep (ESES) and Landau–Kleffner, management should be centered around the proper control not only of seizures but also EEG abnormalities from the beginning, because this strategy – associated with language rehabilitation – offers the best results in terms of epileptic and neuropsychological outcome.

The prognosis of genetic or presumably genetic generalized epilepsies of childhood and adolescence (formerly dubbed as idiopathic) is generally favorable, and recent papers have contributed to specify outcomes in the different syndromes in sufficient detail.

Both CAE and JAE have favorable outcome, with remission rates ranging from 89 % (2 year remission) and 82 % (5 years) for CAE and from 87 % (2 yrs) to 75 % (5 yrs) for JAE [33].

For both types of absence epilepsy, normal intelligence and normal neurologic examination were positive prognostic predictors, whereas the

presence of myoclonic and generalized tonic–clonic seizures were negative ones [33]. However, relapse upon AED withdrawal is different. In CAE, AED withdrawal is advisable and it may be successful in patients in remission with a normalized EEG. By contrast, JAE is a life-long condition, with very poor if any chance of successful withdrawal, even if absence seizures tend to become less severe with age [33]. Classification criteria are in any case of pivotal importance for a correct prognosis. In an Italian study, patients classified as CAE according to the 1989 ILAE criteria entered 1 year remission in only 51 % and relapsed upon AED withdrawal in 22 % of cases, whereas patients included as CAE with more stringent criteria (according to Panayiotopoulos) had remission in 82 % of cases and no relapse upon AED withdrawal [34]. In addition, in contrast to epilepsy prognosis, psychological outcome is poor even in CAE, in terms of intelligence quotient, social difficulties, rates and levels of employment.

Response of JME patients to therapy is also very good, and VPA is effective in about 90 % of patients. Clinical course may be complicated by the occurrence of non-convulsive or myoclonic SE in up to 35 % of patients [35], which may occur upon reduction or change (e.g., VPA to LMT) of AED treatment, but it is in general very favorable. Janz reported that 75 % of patients were in 2 year remission [36], a figure very similar (78 %) to that of Camfield and Camfield [35], myoclonic seizures tended to decrease around the fourth decade of life, and true AED resistance was present in 16 % of patients only [33]. Long-term outcome, however, may be considered poor, as JME patients require a life-long therapy, and withdrawal may not be appropriate for the very high risk of relapse (in up to 90 % of cases). Also for JME, as in absence epilepsy, proper classification is of pivotal importance for long-term prognosis. A minority (5 %) of classic JME patients (representing about ¾ of all JME cases) may achieve terminal remission off treatment, whereas in all other patients (CAE of JAE evolving in JME, and JME astatic, ¼ of all JME cases) remission on AED therapy is rare and no successful AED withdrawal was reported [37]. As in absence epilepsies, JME patients tend to have poor social prognosis, as 75 % have at least one major unfavorable social outcome (behavioral problems at school, low employment rates, unplanned pregnancies, and social isolation) [37].

Regarding other forms of idiopathic generalized epilepsy, long-term outcome is poor in eyelid myoclonia with absences (EMA), with persistence of seizures despite multiple AED treatments [38], but it is much more favorable in epilepsy with grand mal on awakening and grand mal at random [39]. Recent data indicated that remission rates were significantly higher in patients older than 65 (about 75–80 %) than in those younger than 55 years of age (about 35 %), leading to the conclusion that AED withdrawal might be justified in both forms with increasing age and treatment duration [39]. Conflicting data on psychosocial outcome were reported, favorable in one study (50 % of patients with a university degree, 90 % regularly employed for their lifetime) [38], much more negative in another (in terms of high-school graduation, unplanned pregnancies, social isolation, and unemployment) [35].

Epileptic constellations: Prognosis is unfavorable for the epileptic constellations described above. In mesial TLE associated with hippocampal sclerosis or MTS, AED-related remission of seizures is obtained in only 10–40 % of patients [40–41], i.e., figures lower than those usually reported for the localization-related epilepsies.

Factors possibly predicting medical intractability include high-frequency seizures before treatment, EEG interictal abnormalities, and early epilepsy onset. For their low chances of obtaining seizure remission, these patients should be offered the possibility of epilepsy surgery early.

Gelastic seizures related to hypothalamic hamartomas represent a difficult medical problem, since they are very often non-responsive to AED treatment and conventional surgery techniques provide poor outcomes with the potential for significant morbidity. Recently developed surgery techniques such as MRI-guided stereotactic laser ablation [42] could represent a safer and more effective alternative to conventional surgery.

Moreover, the management of epileptic patients with Rasmussen encephalitis can pose dramatic issues to clinicians: AED therapy is of very limited efficacy, long-term immunotherapy may delay neurological deficits but it has incomplete effect on seizures, and hemispherectomy/hemispherotomy could provide seizure freedom but at the price of irreversible neurological deficits. Given that the severity of symptoms varies among different patients and phases, the therapeutic strategy must be tailored to the needs of individual patients, and particular care must be given to properly inform affected patients and their parents [8].

Focal epilepsy of adulthood (both related to structural lesions: formerly symptomatic or, of unknown cause, formerly cryptogenic).

The *prognosis* of this group of epilepsies has received no overt attention by the epilepsy literature. Classic longitudinal cohort studies ([18], for review) clearly demonstrated that a diagnosis of symptomatic or cryptogenic epilepsy, i.e., encompassing the large group of focal epilepsies of adulthood, was a negative predictor of outcome. In other words, they had worse long-term outcome than, for instance, idiopathic epilepsies. Aside from that, available studies specifically addressing the issue of long-term outcome of focal epilepsies of adulthood are lacking. It is known that focal epilepsies related to specific etiologies (e.g., focal cortical dysplasia) possess an intrinsic highly epileptogenic potential, dictating drug refractoriness in most cases and the need of an early (in most cases successful) surgical removal. In most other forms of focal epilepsy, regardless the underlying cause, the long-term prognosis can be predicted from the course of epilepsy of the single individual patient in the few years after onset rather than from the precise diagnosis or classification at the clinical onset [43].

Despite the fact that the extent of natural remission in epilepsy is unknown and remains a largely unresolved issue (studies comparing randomly selected treated *vs* untreated cases from the onset are neither ethical nor easy to conduct in western countries), some general rules have emerged from studies specifically addressing prognosis in epilepsy (see [18] for review).

First, early response to AED treatment is a good parameter, albeit not an absolute parameter, for long-term prognosis.

Second, likelihood of long-term remission is much better in newly diagnosed than in chronic epileptic patients.

Third, the longer the patient is in remission, the less likely seizure will recur in that patient.

Fourth, clinical factors associated with poor long-term outcome (in addition to specific syndromes or symptomatic epilepsies that have already been mentioned in this chapter) are:

(a) The presence of neurologic and mental deficits.
(b) High frequency of seizures before therapy is started.
(c) Most probably, the persistence of interictal EEG abnormalities.
(d) Poor pharmacologic response to initial therapy.

Regarding this latter point, it is rather simplistic to think that once focal epilepsy becomes chronic or fails to respond to two or three AEDs, there are minimal chances of treatment response. An interesting paper has recently demonstrated that, in 155 patients with chronic epilepsy, repetitive drug changes determined 1-year seizure remission in 28 % [30]. Moreover, clinicians should be cautious in defining a patient as inherently drug refractory, since it is a common clinical experience to follow patients whose epilepsy is refractory at the beginning but later remits, or, by contrast, patients well-controlled initially who relapse later on, or patients, although a minority, with a remitting-relapsing pattern of epilepsy [43]. Finally, it has not been consistently demonstrated that etiology is an important predictor of outcome. Even if some lesions with an intrinsically high epileptogenic potential have poor long-term outcomes, the prognosis may be quite variable for the great majority of symptomatic focal epilepsies.

Another important factor should be mentioned, i.e., the role of repeated seizures themselves in dictating prognosis. The notion that "seizures beget seizures" [44] is a long-debated and still unresolved issue. However, longitudinal MRI studies have recently demonstrated pro-

gressive neocortical atrophy in patients with drug-resistant TLE distinct from that due to normal aging, likely representing seizure-induced damage [45], and data from FCD surgical samples have provided support to the hypothesis that epilepsy itself could alter morphology and function in the malformed epileptic brain [46]. Therefore, in managing each single individual patient, the harmful potential of repeated, uncontrolled seizures should always be kept in mind.

Epilepsy in the older patient A final consideration must be made for epilepsy occurring in the elderly. Although it is generally perceived that older patients have higher recurrence rates and much greater risk of seizure-related injuries, and that, therefore, they need early treatment, a recent study from Australia has demonstrated that patients over age 65 had significantly fewer seizure-related injuries than patients younger than 65 [47]. Therefore, age per se is definitively not a risk factor for recurrence. Rather, decision concerning treatment should be based on predictors of recurrence such as symptomatic etiology, seizures occurring during sleep, EEG abnormalities, and focal seizures.

24.10.5 Prognosis of Surgical Treatment

(a) *Standard resection*. Neurologic sequelae of cortical resections occur in about 5 % of cases (hemiparesis, visual field defects, deficits of third and fourth cranial nerves, language defects), but they are transient in 60 % [48]. Mortality is either very low or not reported. Antero-mesial temporal lobectomy is the most used technique, with best outcome. Seizure-free patients (i.e., not experiencing even subjective auras, Engel class I) range between 70 % [49] and 80 % [50] provided that presurgical selection was correctly carried out.

Regarding extra-temporal surgical cortectomies, experience is much more limited, published series include fewer patients, and presurgical SEEG studies may be not conclusive. In general, they have worse outcome. However, the presence of a structural lesion, coinciding with the epileptogenic area, and the possibility of removing the epileptogenic area completely, with no adjunctive neurologic defects, are favorable prognostic factors.

In frontal and parietal lobe epilepsy surgery percentages of post-operative seizure-free patients are about 40–50 % of cases [51, 52], without significant differences between the location of the epileptic focus.

In occipital lobe epilepsy, only 1/3 of surgically treated patients become seizure free [53].

Seizure recurrence after surgery may happen shortly thereafter (early recurrence, in the first 6 months). This is a predictor of bad outcome and persistence of intractable epilepsy [54]. Reasons for failure include the existence of a second distant focus, poor localization of the epileptogenic area, and cases of extra-temporal epilepsy.

Surgery failure is frequently associated with presurgical invasive EEG studies, simply because they are typically used in less well-defined epilepsies. In these cases a further presurgical study might be indicated, possibly leading to second surgery. Later seizure recurrences, usually presenting after at least one year, are usually easier to control with AED medical therapy.

Predictors for bad outcome include normal appearing excised cortex and type I FCD. It has been suggested that cortical areas surrounding the epileptogenic areas removed by surgery may represent a kind of "dormant pro-epileptic" tissue, which can slowly evolve into an epileptogenic one.

A recent, extensive review [55] has shown that 80 % of patients with epilepsy related to glioneuronal tumors (gangliomas and DNETs) were rendered seizure free (Engel class I).

Favorable predictors include short duration of epilepsy, absence of secondarily generalized seizures, complete lesion removal, and, in temporal lobe tumors, extended resections, involving hippocampus, amygdala, and/or the temporal neocortex. No significant differences were demonstrated between adults and children. No extensive data on outcome after AED discontinuation are available.

Surgery of cavernous angiomas may be successful in a high percentage (about 95 %) cases. Favorable prognostic factors include short lasting epilepsy, single or rare seizures, focal seizures only, complete resection extended to the hemosiderin ring, and the presence of small malforma-

tions. In the case of long-lasting epilepsy, secondarily generalized seizures, large-size angiomas, and incomplete excision, the outcome is less favorable (around 60–70 %).

(b) *Hemispherectomy and hemispherotomy*. Hemispherectomies, involving the complete ablation of one cerebral hemisphere, are now rarely performed because of the high risk of mortality related to hydrocephalus and hemorrhage in up to 6–7 % of cases. Late complications include hemosiderosis, hydrocephalus, and neurologic deterioration in up to 20 % of cases [56]. Patients may achieve seizure control in 80–90 % of cases. Hemispherectomy is now largely replaced by the much less dangerous hemispherotomy, consisting of a variable amount of cortical removal associated to hemisphere disconnection. Complications include hydrocephalus in less than 3 % of cases, bleeding in less than 2 %. The outcome, if patients are adequately selected, can reach the ratio of 90–100 % seizure-free patients [57].

(c) *Callosotomy*. A disconnection syndrome, characterized by alexia, unilateral apraxia, and tactile anomia is frequently associated with complete callosotomy. Another common complication is mutism, which is however transient (lasting 1–10 days) in the case of anterior callosotomy sparing the splenium. Drop attack seizures are reduced significantly or disappear in 50–80 % of patients [31].

(d) *Neuromodulation*. The outcome of VNS, according to a recent meta-analysis [58], is 50 % reduction of seizures in about 50 % of patients. Data do not allow identifying best candidates, even if children show a trend to better results, more frequently in those younger than 6 years. Patients with tuberous sclerosis or post-traumatic epilepsy show better outcome.

Data on DBS are scarce, the only significant study being a recent multi-center, double-blind, and randomized trial of stimulation of the anterior thalamic nuclei in focal refractory epilepsy [59]. After 2 years of stimulation, seizure frequency was reduced by 56 % in 54 % of patients, seizure severity was reduced and quality of life improved. No data on best candidates were available.

24.10.6 Disability

Outcome in epileptic patients may greatly vary not only regarding seizure persistence and frequency, but also in terms of neurologic and mental/cognitive outcome. As illustrated in the "Clinical features" section, childhood epilepsy can develop in healthy subjects, with complete recovery and no consequences on psychomotor development (FS^+, BECT, Panayiotopoulos syndrome, CAE). In other cases, previously normal children may present an epileptic encephalopathy, possibly resulting in death, or in a combination of refractory epilepsy and severe psychomotor regression (Ohtahara, West syndrome). Similar encephalopathic clinical features can be present in children as symptoms of different diseases, such as perinatal vascular lesions, tuberous sclerosis, cerebral malformations, and genetic diseases. In these cases, disability may be the consequence of both the underlying disease and the subsequent seizures. The presence of very active EEG epileptiform abnormalities can severely affect child development and behavior, as in ESES or Landau–Kleffner syndrome. EEG normalization achieved through an adequate AED treatment usually leads to significant cognitive improvement in the affected children.

Regarding seizures, the type, duration, symptomatology, and wakefulness or sleep recurrence are all factors governing the degree of disability.

Among focal seizures, the presence, degree, and duration of loss of contact, as well as associated socially unacceptable behaviors (sphincter control, psychomotor agitation) all dictate seizure negative impact on everyday life, whereas seizures characterized by subjective symptoms only are the least disabling.

Among generalized seizures, high-frequency absence seizures can negatively affect the child's cognitive development; nocturnal seizures, even if tonic–clonic, are usually less disabling, whereas fall determining seizures, particularly when of sudden nature, are the most disabling, for the high risk of subsequent brain trauma and wounds.

Moreover, the patient's personal, working, and social histories are relevant factors in seizure-related disability. Some job occupations are greatly affected by seizure-related risk of fall and

loss of consciousness, and limitations of driving, Obviously, people with a normal working and social life could be very upset by seizures determining loss of contact and uncontrolled automatisms, interrupting them during a telephone call, a conference, or when visiting a patient. Similar seizures could be of more limited relevance in neurologically impaired patients. Therefore, epilepsy treatment must be tailored on the specific needs of each individual patient.

Finally, social outcome can be affected deeply by seizures, but it is not necessarily related to seizure control, as specific epilepsy syndromes might be associated with bad social outcome even if seizures are completely controlled (see above). Ideally, every epilepsy patient should always be encouraged to lead a fully normal life, be properly psychologically assisted, and properly advised on laws protecting their clinical condition and/or associations specifically dedicated to social integration.

24.11 Non-epileptic Myoclonus

24.11.1 Definition

Myoclonus is a sudden, brief (mostly <100 ms), jerky, shock like involuntary movement, synchronous on antagonist muscles.

24.11.2 Features

It may be positive, when determining muscle movements, or negative, when interrupting them. It cannot be suppressed voluntarily. Myoclonus can be of epileptic nature, when determined by a cortical activation, with a corresponding EEG correlate, as in many epileptic syndromes illustrated above.

24.11.3 Differential Diagnosis

Differential diagnosis between myoclonic and clonic seizures can be difficult in some cases because a single jerk can be a fragment of a clonic seizure.

Myoclonic seizures are single, or irregularly recurrent events, whereas clonic seizures are rapid rhythmically recurrent events [60]. In some cases of epileptic myoclonus, as in some PMEs, the correlation between myoclonic jerks and EEG discharges or abnormalities might be unclear, but accurate studies, such as back-averaging EEG analysis, reveal the cortical origin of many myoclonic movements.

24.11.4 Pathogenesis

In addition to the cortex, myoclonus can be generated at several levels of the nervous system. In general, cortical myoclonus is mostly epileptic. It is usually generated in the frontal or prefrontal cortex, as in the case of focal myoclonus, and etiologically determined by an underlined lesion. In idiopathic generalized epilepsies, myoclonus is generalized, even if neurophysiology studies have revealed that the activation of rather restricted frontal and temporal cortical networks is sufficient to induce discharges in JME.

Non-epileptic subcortical myoclonus is usually bilateral, with longer muscle contractions, up to 500 ms. It can be provoked by external stimuli, such as noise, voluntary action, or simply intention to movement (Lance-Adams syndrome), and it may originate from diencephalic or reticular regions.

Non-epileptic propriospinal myoclonus is a rare movement disorder generated in the spinal cord, provoked by different spinal lesions and affecting muscles innervated by adjacent spinal segments [61]. Propriospinal myoclonus occurs in middle-age male patients, it involves the abdominal wall muscles, and it is worsened by the lying position and the wake-sleep transition. DTI-FT detects spinal cord abnormalities in all patients. CZP is the most effective drug, and ZNS a possible alternative option [62].

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Neoplastic Disorders

25

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Abbreviations

AA, Anaplastic astrocytomas; AEDS, Antiepileptic drugs; ADC, Apparent diffusion coefficient; BMTS, Brain metastases; CHT, Chemotherapy; CNS, central nervous system; CSF, cerebrospinal fluid; DWI, Diffusion weighted MR; FDA, Food and Drug Administration; GBM, Glioblastoma multiforme; GC, Gliomatosis cerebri; HDAraC, High dose cytosine arabinoside; HDMTX, High dose methotrexathe; HGG, High-grade gliomas; IELSG, International Extranodal Lymphoma Study Group; KPS, Karnofsky performance status; LGG, Low-grade gliomas; MRI, magnetic resonance imaging; MTX, Methotrexate; MGMT, O6-methylguanine-DNAmethyltransferase; NHL, Non-Hodgkin lymphoma; NM, Neoplastic meningitis; OS, Overall survival; PCNSL, Primary CNS lymphoma; PCV, procarbazine-CCNU- vincristine; PFS, Progression-free survival; rCBV, Regional blood flow on perfusion imaging; RPA, Recursive Partitioning Analysis; RS, Radiosurgery; RT, Radiotherapy; SRS, Stereotactic radio-surgery; SWI, Susceptibility-weighted imaging; TMZ, Temozolomide; WBRT, Whole-brain radiotherapy; WHO, World Health Organization

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Key Points

- **Definition**
  - **CNS tumors** – Heterogeneous population of benign or malignant neoplasms
  - Brain tumors account for 85–90 % of primary tumors of CNS. Benign tumors are usually curable, but may be life threatening. Malignant tumors grow rapidly and crowd or invade the nearby brain tissue. Mortality rate from malignant brain tumors is very high.
- **Diagnostic markers** – Symptoms and signs of brain tumors depend on their size, type, and location.
  - Common presenting manifestations include headache, seizures, and altered mental status.
  - Primary brain tumors do not spread outside of the CNS.
  - MRI is the first choice examination; biopsy is often required to confirm the diagnosis.
- **Pathology** – WHO grading system classifies CNS tumors into specific histological categories. The most common primary adult brain tumors are gliomas and meningioma. Twenty to forty percent of brain tumors are metastatic.
- **Prognosis and Treatment**
  - Prognosis depends on:
    - Type of tumor (histology)
    - Location and size of tumor
    - Tumor grade
    - Patient's age and performance status
      - *Genetic*
  - MGMT DNA-repair gene silencing: independent positive prognostic factor
- **Survival**
  - LGG: 5-year overall survival 58–72 %; progression-free survival 37–55 %.
  - GBM: 5-year survival rate <5 % (); 10 % (AA); 85 % (anaplastic oligodendroglioma and anaplastic oligoastrocytoma).
  - Gliomatosis survival rates: 48 % at 1 year, 37 % at 2 years, 27 % at 3 years.
  - Ependymomas: 5-year OS for adults with intracranial lesions is 60–85 %.
- **Brain metastases (BMTS)**
  - Recursive Partitioning Analysis (RPA) identifies OS in 3 classes of patients.
  - The most favorable: patients <65 years with well-controlled extracranial disease and a Karnofsky performance status ≥70 (RPA class 1, median OS = 7.1 months). Patients with a Karnofsky performance status <70 were classified as RPA class 3 (median OS = 2.3 months).
  - Patients who did not meet criteria in one of the above classes (RPA class 2, median OS = 4.2 months).
- **Neoplastic meningitis (NM)**
  - Among the solid tumors breast cancer responds best to the treatment (median OS = 6 months; 11–25 % 1-year)
- **Primary CNS lymphoma (PCNSL)**
  - Independent predictors of prognosis: age >60 years, ECOG performance status >1, increased serum LDH level, increased CSF protein concentration, involvement of deep regions of the brain. Level 0–1 (2-year OS = 80 %), 2–3 (2-year OS = 48 %), 4–5 (2-year OS = 15 %).
- **Meningiomas**
  - Ninety percent of meningiomas are benign (WHO grade I); 75 % of grade I meningiomas have at least 10 years OS, without recurrences.

25.1 Low-Grade Gliomas

25.1.1 Definition

- Low-grade gliomas (LGGs) are a group of slow-growing primary intra-axial CNS tumors, originating from glial cells.
- Clinically, histologically, and molecularly heterogeneous, LGGs are classified by the World Health Organization (WHO) as:
  - *Grade I* (pilocytic astrocytoma, dysembryoplastic neuroepithelial tumor, pleomorphic xanthoastrocytoma, and ganglioglioma).
  - *Grade II* (astrocytoma, oligodendrogliomas, oligoastrocytoma, ependymoma).

25.1.2 Epidemiology

- LGG accounts for approximately 10–20 % of all primary brain tumors in adults and 25 % in children.
- Astrocytomas are preponderant, even if there is an apparent increase in the incidence of mixed oligoastrocytomas and oligodendrogliomas in recent years.
- The highest incidence of these group of tumors is between 35 and 44 years of age [1]

25.1.3 Clinical Features

- Symptoms usually depend on the size and location of the tumor and whether it has infiltrated into other areas of the brain or spine.
- Seizures are often the first sign of a low-grade glioma (72–89 % of patients), and these can often be resistant to therapy.
- Mental status changes or increased intracranial pressure signs, such as headache and nausea, are both possible symptoms, and focal neurological deficits present in 2–30 % of patients.
- Patients may have normal neurological examinations.

25.1.4 Pathology

- The more common subtypes are diffuse astrocytomas and oligodendrogliomas. Diffuse astrocytomas include fibrillary, protoplasmic, and gemistocytic variants; the mitotic activity in this group of tumors is low.
- Mixed gliomas consist of mixtures of various tumor subtypes (such as diffuse astrocytoma and oligodendroglioma). These tend to behave similar to diffuse astrocytomas.
- In general, it is important to note that the group of low-grade diffuse astrocytomas (especially the gemistocytic variant) have a tendency to become more histologically and clinically severe over time, progressing towards anaplastic astrocytomas and finally glioblastoma multiforme.

25.1.5 Diagnostic Markers

- *CT* usually demonstrates an area of hypodensity with calcifications in 20 % of diffuse astrocytomas and 40 % of oligodendrogliomas.
- *MRI* shows a relatively well-defined, usually homogeneous mass that displays little or no mass effect, and minimal or no vasogenic edema and enhancement (Fig. 25.1).
- *MRI* (diffusion weighted) can show higher apparent diffusion coefficient (ADC) due to low cellularity and low regional blood flow on perfusion imaging (rCBV). Metabolism and proliferation (assessed by MR spectroscopy or PET) are usually normal or lower than normal brain in LGG.

25.1.6 Treatment

- The optimal treatment and the exact timing of treatment in LGG is still controversial, and the risks and benefits of therapies must be carefully balanced with the data available from limited prospective studies.
- Symptoms management requires different therapeutic approaches.
- The treatment is based on:

1. Surgery
   - The objective is the maximal possible resection (patients with gross total resection have the longest survival), minimizing the postoperative deficits. Total resection improves seizure control, particularly in patients with a long epileptic history and insular tumors.
   - When surgery is not feasible, a biopsy is performed to obtain a histological diagnosis.
2. Radiotherapy
   - The RT treatment after surgery is still a topic of debate, in particular regarding the optimal timing of treatment and the optimal radiation dose.
   - The lack of survival benefit with immediate adjuvant radiotherapy has been used as a justification to postpone radiation until disease progression.
   - Randomized trials showed no advantage for higher versus lower doses of RT (standard total RT dose of 50–54 Gy).
3. Chemotherapy
   - It is an option for the initial treatment of patients with large residual tumors after surgery or unresectable tumors; it is also an option for patients with recurrence after surgery and radiation.

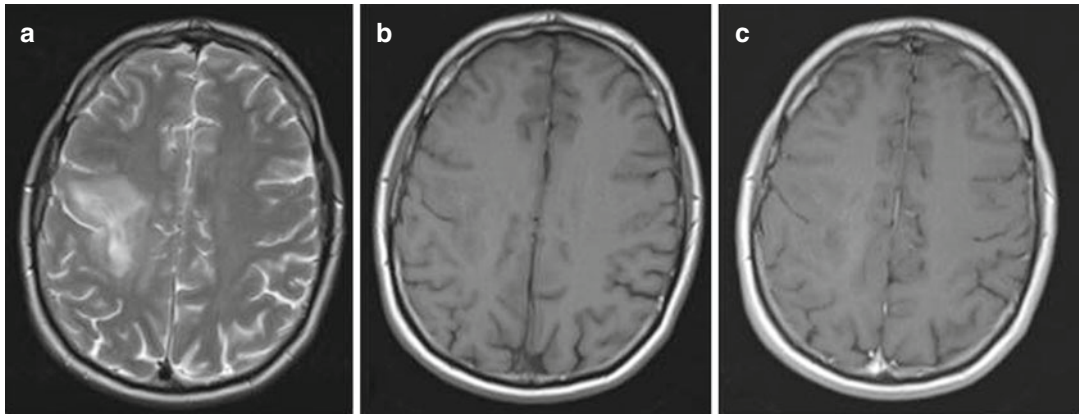

Fig. 25.1 Astrocytomas grade II. Axial MRI images show a lesion hyperintense in T2 sequences without mass effect (**a**), slightly hypointense in T1 sequences (**b**) without contrast enhancement (**c**) located in right posterior and inferior frontal lobe

- Observational studies indicate that chemotherapy may be effective in patients with oligodendroglial tumors; its role in diffuse low-grade astrocytomas is less clear.
- PCV chemotherapy after radiation in high risk low-grade glioma could improve survival rates (median OS 13.3 years vs 7.8 years).
- Due to its favorable toxicity profile, TMZ has been proposed as a therapeutic alternative to radiotherapy in first-line treatment, especially when patients are young, or tumor growth would require too extensive a field of radiation.
- Prognostic biomarkers could be very important in therapeutic decisions.

25.1.7 Prognosis

- 5-year overall survival (OS) and progression-free survival (PFS) rates range from 58 to 72 % and 37 to 55 %, respectively.
- Two biological characteristics prominently influence the prognosis of low-grade gliomas.
  - A propensity to infiltrative growth is virtually seen in all low-grade gliomas (except WHO grade I gliomas).
  - A propensity to malignant progression: more than 50 % of low-grade gliomas could transform into anaplastic gliomas [1, 2].

Positive prognostic factors that can influence survival include:

- Histology: Oligodendrogliomas show a better prognosis than astrocytomas; the prognosis of patients with gemistocytic astrocytomas is worse than that of the average astrocytoma patient.
- Younger age (<40 years).
- Better performance status (KPS) at diagnosis and the absence of preoperative neurological deficits.
- The lack of contrast enhancement on MRI, since tumor size or location is not universally accepted.
- The extension of resection.
- Molecular features: 1p deletion or 1p/19q codeletion is a favorable marker both in oligodendroglioma and oligoastrocytoma; IDH1 mutation has been recently suggested as an independent favorable prognostic factor [1].

25.2 High-Grade Gliomas

25.2.1 Definition

High-grade gliomas (HGGs) comprise: glioblastoma, World Health Organization (WHO) grade IV, anaplastic astrocytoma (WHO grade III), mixed

anaplastic oligoastrocytoma (WHO grade III), and anaplastic oligodendroglioma (WHO grade III).

25.2.2 Epidemiology

The annual incidence of HGG is approximately 5/100,000. Glioblastomas (GBM) account for 60–70 % of HGG, anaplastic astrocytomas (AA) account for 10–15 %, and anaplastic oligodendrogliomas and anaplastic oligoastrocytomas account for 10 %.

HGGs are more common in men and twice as common in whites than in blacks. The median age at diagnosis is 64 years (GBM) and 45 years (AA)

No underlying cause has been identified for the majority of malignant gliomas. The only established risk factor is exposure to ionizing radiation.

Less than 5 % of patients affected by malignant gliomas have a family history of gliomas. Some of these familial cases are associated with rare genetic syndromes, such as neurofibromatosis 1 and 2.

25.2.3 Clinical Features

Symptoms of HGGs are the same of other brain tumors. Clinical manifestations include general symptoms due to increasing pressure in the brain (ICP) and focal symptoms and signs reflecting the size and location of the tumor.

In high-grade tumors, the incidence of epilepsy (30–40 %) is lower compared to low-grade gliomas (72–89 %).

Cognitive deficits are common and frequently may include slowed thinking, memory loss, and difficulty with multitasking.

25.2.4 Pathology

- Gliomas arise from astrocytes, oligodendrocytes, or their precursors. Gliomas are graded, according to the four-tier WHO system (I to IV). Grading is based on pathologic features, endothelial proliferation, cellular pleomorphism, mitoses, and necrosis.
- The high-grade gliomas are extremely invasive, with tumor cells often found up to 4 cm away, even on the contralateral side of the brain.

25.2.5 Radiographic Findings

MRI is the standard imaging. It is highly sensitive for a brain tumor but not specific (see Table 25.1).

25.2.6 Differential Diagnosis

- Brain Metastases
- Primary CNS Lymphoma: usually shows homogeneous enhancing.
- Cerebral Abscess: smooth and complete susceptibility-weighted imaging (SWI) low-intensity rim, central restricted diffusion is helpful.
- Demyelinating tumefactive lesions (MS): younger patients, often open enhancement ring.
- Subacute cerebral infarction: normal choline and rCBV.

25.2.7 Prognosis

The outcome for HHG remains dismal despite multimodality treatments, including surgery, chemo-radiotherapy.

Estimates of survival rates vary widely according to the type of tumor: the 5-year survival rate for GBMs is less than 5; 10 % for AA, and finally, for anaplastic oligodendroglioma and anaplastic oligoastrocytoma, the rate is 85 % or better.

Positive prognostic factors that can influence survival include:

- Histology: Oligodendroglial tumors show a better prognosis than astrocytomas; the prognosis of patients with gemistocytic astrocytomas is worse than that of the average astrocytoma patient.

Table 25.1 Main radiological features of LGG, HGG, brain metastases, meningiomas, and PNLS

	LGG	GBM	Brain MTS	Meningiomas	PNSL
T1WI	Usually Iso/hypointense, well-defined mass	Irregular hypointense, isointense, necrosis cyst common. Ring enhancement surrounding central necrosis	Hypointense, isointense, hyperintense or mixed Strong enhancement, variable patterns	Extrassial lesions, isointense to cortex with homogeneus and strong enhancement	Homogenous iso/ hypointense to cortex Strong homogenous contrast enhancement, (non-enhancing in less than 10 %)
T2WI/FLAIR	Homogenous, hyperintense, no/little mass effect	Heterogenous, hyperintense, necrosis cyst, surrounding edema and infiltrating (nonenhancing) tumor	Variable, usually moderate hyperintense to cortex , surrounding edema	Iso-hyperintense to cortex	Homogenous iso/ hypointense, may be heterogenous from necrosis
DWI	No restricted diffusion	No restricted diffusion	Usually no restricted diffusion	Atypical and malignant variants show restricted diffusion	Restricted diffusion
Perfusion	Low rCBV values	High rCBV in tumor and peritumoral region	High rCBV values	elevated rCBV values	Low rCBV values
MRS	Low choline peak, low NAA, low values of Lac and lipids	Elevated choline peak, decrease in Cho/NAA and Cho/Cr ratios. High value of Lac and lipids	Strong Cho peak, NAA decreased, elevated lipid peaks without significant NAA/Cr and Cho/Cr ratios	Elevated choline and alanine peak	NAA decreased, elevated lipid peaks and high Cho/Cr ratios

- Younger age (<40 years).
- Better performance status (KPS) at diagnosis and the absence of preoperative neurological deficits.
- The extension of resection; tumor diameter <6 cm; tumor not crossing midline.
- Molecular features: 25–50 % of anaplastic oligodendrogliomas and oligoastrocytomas harbor 1p/19q codeletion, which are favorable markers in oligodendroglioma and oligoastrocytoma. IDH1 mutation has been recently suggested as an independent favorable prognostic factor in these tumors.
- O6-methylguanine-DNAmethyltransferase (MGMT): the epigenetic silencing of the MGMT DNA-repair gene by promoter methylation is an independent prognostic factor in patients with glioblastoma and has been associated with longer survival in patients who receive alkylating chemotherapies.

25.2.8 Treatment and Prognosis

- Corticosteroids are extensively employed in HGG (usually dexamethasone, 4–16 mg/day) to relieve edema.
- Antiepileptic drugs (AEDs) prophylaxis should not be routinely used. Moreover, some AEDs interfere with chemotherapeutic agents. Levetiracetam (1000–2000 mg/day) may be considered as a first-line agent; enzyme-inducing AEDs (phenobarbital, carbamazepine, phenytoin) should be discouraged.

Surgery: for either diagnosis or tumor-debulking purpose. The general target is to remove more than 90 % of the tumor volume. Maximal cytoreduction without causing neurological deficits has critical prognostic value for patient outcome and survival.
  - For HGG located in eloquent areas of the brain or for patients with poor performance status, a biopsy of the tumor could be more appropriate.
  - Functional MRI is increasingly used in the planning of surgery in eloquent areas. Intraoperative MRI is now standard practice in some selected centers.

Radiotherapy: Fractionated focal radiotherapy (60 Gy, 30–33 fractions of 1.8–2 Gy) is the standard treatment after resection or biopsy. Ninety percent of tumors recur within a 2-cm margin. The current practice is to irradiate the tumor-involved tissue with an additional 2-cm margin.

Chemotherapy: After surgery, adjuvant radiotherapy combined with the DNA alkylating agent temozolomide should be considered in all glioblastomas. Temozolomide is administered orally (75 mg/m^2), concomitantly with radiotherapy, followed by an adjuvant course (150–200 mg/m^2 for 5 consecutive days every 28 days for 6 cycles).
  - Adjuvant and concomitant temozolomide combined with radiation gives significant improvements in median progression-free survival over radiation alone (6.9 vs 5 months), overall survival (14.6 vs 12.1 months), and the likelihood of being alive in 2 years (26 % vs 10 %).
  - Patients with glioblastomas displaying promoter methylation (MGMT) are more likely to benefit from the addition of temozolomide to radiotherapy.
  - The other first-line treatment approved by Food and Drug Administration (FDA) is biodegradable polymers containing the alkylating agent carmustine (Gliadel) implanted into the tumor bed after its resection.
  - According to the prospective randomized Radiation Therapy Oncology Group (RTOG) and EORTC trials on the role of PCV chemotherapy (procarbazine, CCNU, and vincristine) plus radiation in newly diagnosed anaplastic oligodendroglioma and oligoastrocytoma tumors, patients with 1p/19q codeletion survive much longer than patients with non-codeleted tumors (OS 123 vs 23 months in the EORTC study). Moreover, 1p/19q codeletion predicts sensitivity to PCV chemotherapy.
  - Many oncologists prefer temozolomide for anaplastic gliomas because it has fewer side effects than PVC and is easier to administer.

25.2.9 Treatment at Recurrence

- All HGG patients experience disease recurrence. None of the existing salvage treatments has significantly improved their survival; some benefits have been observed only in selected patients.
- A new tumor resection and cytoreduction could be considered for mass effect relief. At the moment, data concerning survival benefits are not conclusive
- Salvage chemotherapy options include temozolomide rechallenge and nitrosoureas (in the US, Bevacizumab is a frequently used treatment for recurrent glioblastoma). Bevacizumab often results in rapid decrease of peritumoral edema, and it is an option for highly symptomatic patients, but survival benefits are less clear.

25.3 Gliomatosis

25.3.1 Definition and Pathology

The 2007 WHO classification defines gliomatosis cerebri (GC) as a subtype of diffuse glioma, considering it as a growth pattern of astrocytomas (most commonly), oligodendrogliomas, and oligoastrocytomas, in which invasion by glial neoplastic cells involves more than three lobes [7].

Molecular alterations found in GC are usually the same as in other low-grade tumors.

25.3.2 Epidemiology and Clinical Features

- Same age and sex distribution of other gliomas; GC is usually found in the age group of 40–50 years and presents a slightly higher male prevalence
- Symptoms might appear slowly and subtly and are variable and not specific

25.3.3 Diagnostic Markers

- *MRI* is the first choice: T2 weighted images demonstrate the tumor involvement trough the white matter in multiple lobes with loss of distinction between grey and white matter
- Contrast enhancement is not usually evident or minimal (if present, could indicate a malignant transformation)

25.3.4 Treatment and Prognosis

- Prognosis is poor, probably due to the highly infiltrative activity of glioma cells. The survival rates at 1-, 2-, or 3 years are 48 %, 37 %, and 27 %, respectively [7], not very different from those of glioblastoma.
- The optimal treatment of GC is still unclear [7]:
  1. The role of surgery is limited to histological diagnosis.
  2. Whole brain radiation therapy alone could affect clinical and radiological response rates positively, but its role on overall survival is questionable.
  3. Chemotherapy seems to be beneficial at least in some patients.

25.4 CNS Embryonal Tumors and Medulloblastoma

25.4.1 Definition

- CNS embryonal tumors include a heterogeneous group of highly cellular, mitotically active, immature-appearing neoplasms.
- The 2007 WHO classification divided these tumors as:
  - Medulloblastoma
  - Supratentorial PNET (neuroblastoma, ganglioneuroblastoma, medulloepithelioma, ependymoblastoma)
  - Atypical teratoid/rhabdoid tumor
- The most common CNS embryonal tumor is medulloblastoma

25.5 Medulloblastoma

25.5.1 Epidemiology and Pathology

- Medulloblastoma is the most common malignant CNS tumor of childhood, comprising 20 % of all pediatric brain tumors but only 0.4–1 % of all adult CNS tumors.
- The current World Health Organization's (WHO) classification recognizes the classic medulloblastoma and four histological variants: anaplastic, large cell, nodular desmoplastic, and medulloblastoma with extensive nodularity (MBEN).
- Risk stratification has been traditionally based on age, metastatic status at diagnosis, and extent of surgical resection. More recently, new molecular data has permitted dividing medulloblastoma into at least four distinct subgroups with distinct genetic profiles, distinct phenotypes, and clinical outcomes: Wnt/Wingless (WNT) group is associated with a better prognosis, Sonic Hedgehog (SHH) group is associated with a worse prognosis, while Group 3 and Group 4 are associated with an intermediate prognosis.

25.5.2 Diagnostic Markers

- A median delay of 2 months may be counted from first symptoms to diagnosis.
- Presenting symptoms are related to the age of patients:
  - In infants: macrocrania, vomiting, and psychomotor regression are the main symptoms.
  - In adults: headaches, vomiting, and gait disturbance frequently lead to diagnosis.
- In children, a well-defined, homogeneous vermian tumor is usually found with intense contrast enhancement.
- In adults, the tumor is predominantly located in the cerebellar hemispheres, and is poorly defined, with enhancement less intense and, possibly, with necrosis/cysts (Fig. 25.2).
- Distant metastases should be carefully searched for (they may occur in 20 % of medulloblastoma at first diagnosis).

25.5.3 Treatment and Prognosis

- The 5- and 10-year overall survival rates are 78 % and 30 %, respectively.
- The treatment of medulloblastoma consists of maximal surgical resection, craniospinal radiation, including a posterior fossa boost, and chemotherapy.

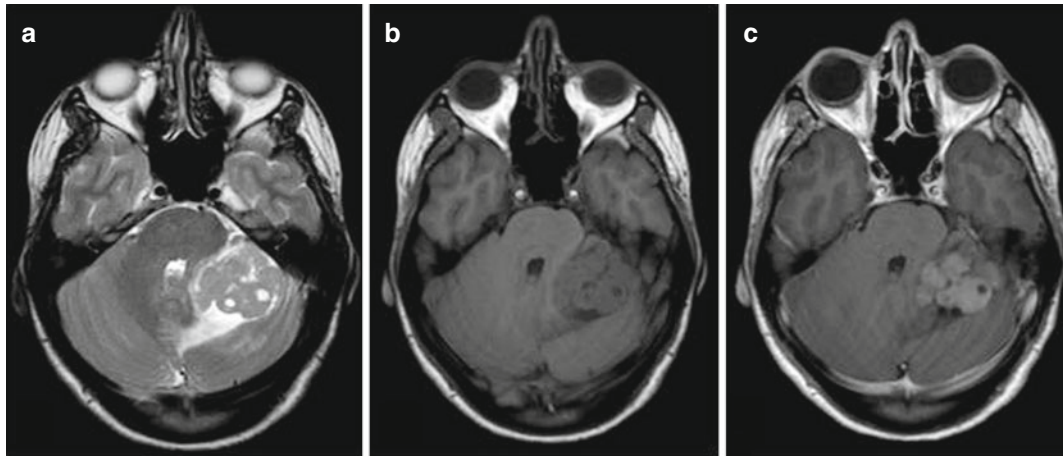

Fig. 25.2 Medulloblastoma. Axial MRI of an adult medulloblastoma in left cerebellar hemisphere shows a relatively dishomogeneous mass (**a**) in T2 sequences, with moderately intense contrast enhancement after contrast medium (**c**)

Surgery
- Gross total surgical resection has been demonstrated to improve outcomes in adults and is the standard of care in initial management.
- Residual tumor of less than 1.5–2 is associated with a better prognosis.

Radiotherapy
- MB is a very radiosensitive tumor.
- Given the aptitude of this tumor to disseminate, especially upon relapse, craniospinal radiotherapy is necessary to maximize survival.

Chemotherapy
- Although chemotherapy is an established and important adjunct that improves survival in poor risk adult medulloblastoma, its role remains equivocal in standard-risk adults.

25.6 Ependymomas

25.6.1 Epidemiology and Pathology

Ependymomas are rare tumors that arise from the ependymal cells of ventricles or spinal cord.

They are the third most common brain tumor in children, representing 10 % of pediatric intracranial tumors, 4 % of adult brain tumors, and 15 % of all spinal cord tumors.

- WHO classification divided these tumors as:
  - Grade 1: subependymoma and mixopapillar ependymoma
  - Grade 2: classic ependymoma (4 variants: cellular, papillar, clear cells, tanycytic)
  - Grade 3: anaplastic ependymoma

25.6.2 Diagnostic Markers

Ependymomas are often slow-growing tumors: signs and symptoms may be due to increased intracranial pressure, and they include changes in brain, function, and seizures.

In children, around 90 % of ependymomas are intracranial, with the majority of these arising from the roof of the fourth ventricle.

- In adults and adolescents, 75 % of ependymomas arise within the spinal canal [8].
- Ependymomas are hypointense to isointense on T1-weighted images and hyperintense on T2-weighted images, with minimal to moderate enhancement.

25.6.3 Prognostic Factors

- The WHO classification has been a subject of controversy regarding its prognostic capabilities.
- The 5-year OS for adults with intracranial lesions is 60–85 %.
- Tumor location has been indicated as a prognostic factor (infratentorial ependymomas seem to have a better prognosis).
- Other potential, better prognostic factors include age <40 years and high Karnofsky Performance Scale status (KPS).
- Spinal ependymomas in adults seem to have a better prognosis.
- Genetic biomarkers as prognostic indicators may allow more individualized therapeutic strategies [8].

25.6.4 Treatment

- There is a large consensus on spinal ependymomas.
  - Surgery at diagnosis
- In intracranial ependymomas:

Surgery
- Maximal safe resection and pathologic confirmation of disease are the main goals of surgery.
- Extent of resection is the main prognostic factor for all subtypes and localizations.

Radiotherapy
- Adjuvant radiotherapy can improve local control as well as overall survival.
- Radiotherapy at recurrence is important.

Chemotherapy
- Has a limited role in the treatment of ependymoma.

– Cisplatin and carboplatin are the single agents most frequently used (responses in about 10 % of patients).

25.7 Metastatic Brain Tumors

25.7.1 Epidemiology and Pathology

- Brain metastases (BMTS) are about 10 times more frequent than primary brain tumors and occur in 20–40 % of cancer.
- Tumors that most frequently metastasize to the brain are: lung cancer (40 % of non-small-cell lung cancer), breast cancer (30–50 % with HER2-positive) unknown primary cancer (10–15 %), melanoma (10 %), and colon cancer (5 %) [9, 10].
- The most common localizations of BTMS are in the gray–white junction of cerebral hemispheres (80 %), 15 % in the cerebellum, and 5 % in the brain stem. BTMS are multiple in more than 50 % cases. Leptomeningeal-pachimeningeal metastases may constitute as much as 9 % of total CNS metastases (Fig. 25.3).

25.7.2 Diagnostic Markers

Signs and symptoms may be due to increased intracranial pressure. Focal neurological deficits and personality changes are common. About 10 % of patients present with hemorrhage. Contrast enhancement MRI is the first choice examination. CT scanning is used widely because of its accessibility (see Table 25.1).

25.7.3 Differential Diagnosis

- Abscess, high-grade gliomas, strokes, demyelinating disease.

25.7.4 Prognosis

- Recursive Partitioning Analysis (RPA) is an algorithm used to identify three classes of patients, which predicts median overall survival (OS). The most favorable outcome is observed in patients under 65 years old with well-controlled extracranial disease and a Karnofsky performance status ≥70 (RPA class 1). Patients with a Karnofsky performance status less than 70 were classified as RPA class 3 and demonstrated a median OS of 2.3 months. Patients who did not meet criteria in one of the above classes (RPA class 2) had a median OS of 4.2 months [9, 10].

25.7.5 Treatment

- Corticosteroids are extensively employed (usually dexametashone 4–16 mg/day) to reduce tumor edema.

Surgery

- The decision whether to recommend surgery should be based on strict criteria such as: number of metastases, expectation of life >3 months, and extracranial oncologic status.
- For patients with limited systemic disease or who have reasonable options for systemic treatment, aggressive management should be considered.
- Surgical resection followed by radiotherapy is an effective treatment for patients with single, surgically accessible, BMTS presenting a controlled extracranial disease and good general condition.
- Multiple cerebral BTMS and/or widespread extra CNS metastases preclude surgery in favor of palliative irradiation as the sole therapy.

Radiation therapy

- The radio-treatment of BTMS includes whole-brain radiotherapy (WBRT) and radiosurgery (RS) in various combinations according to number, size, location of the BMTS, patient's performance status, and previous surgery.
- WBRT is widely used. All patients with more than three metastatic lesions should be treated with WBRT as primary therapy. For symptomatic patients, median survival

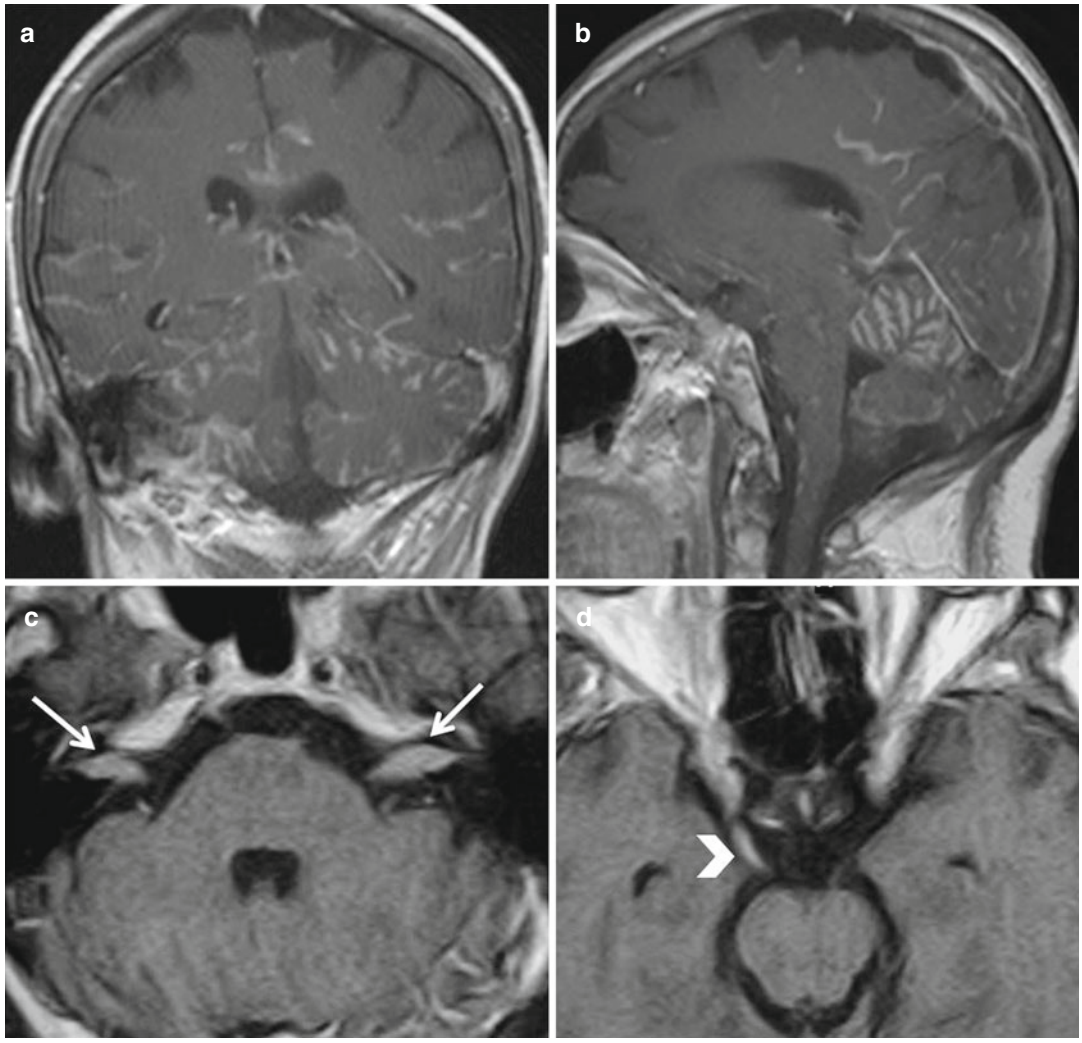

Fig. 25.3 Leptomeningeal carcinomatosis. T1-weighted images post contrast medium. In (**a**, **b**) diffuse leptomeningeal enhancement is seen, mostly along cerebellar folia. Images (**c**, **d**) show enlargement and enhacement of both V° (*arrows*) and right III° (*arrowhead*) cranial nerves

is about 1 month if untreated and 3–6 months if WBRT is delivered, with no significant differences among different radiotherapy fractionation schemes.

- Stereotactic radio-surgery (SRS) alone has been suggested as an alternative both to surgery and to WBRT.

Chemotherapy

- Chemotherapy has a limited role in BMTS, and usually chemotherapeutic agents efficacious for the primary tumor are used.

25.8 Metastatic Spinal Tumors

25.8.1 Epidemiology and Pathology

- Spinal metastasis is the most common tumor of the spine, accounting for approximately 95 % of spinal tumors, mostly in the thoracic region. Each year, 5 % of patients with cancer will develop spinal metastasis.
- The cancers most often metastasizing to the spine are: breast (21 %), lung (14 %), prostate

(8 %), renal (5 %), gastrointestinal (5 %), and thyroid (3 %).
- Usually, the infiltration starts in the posterior half of the vertebral body.

25.8.2 Diagnostic Markers

- For the majority of patients, pain is the first presenting symptom that is not alleviated with rest and is often worse at night.
- Spinal cord compression is the most debilitating complication of spine metastases and is considered an emergency. It affects 5–10 % of all cancer patients. If untreated, neurologic deficits rapidly progress to irreversible spinal cord damage.

25.8.3 Treatment

- Primary goals of treatment are to relieve pain, and to preserve or restore function. Corticosteroids remain a routine initial treatment.

Surgery
- The indications for surgery include spinal cord compression, acute or progressive neurologic deterioration, spinal instability, radioresistant tumors, and life expectancy of at least 3 months.
- Paraplegia lasting for more than 24 h is an exclusion criterion because of the low probability of improvement of neurological deficits.

Radiotherapy
- Radiotherapy is widely used for patients who have radiosensitive tumors, for patients who cannot afford surgery, or have low life expectancy.
- Highly radiosensitive tumors include lymphomas, myelomas, seminomas, and neuroblastomas; breast and prostate cancers are moderately radiosensitive.
- In the absence of compression, fracture, or instability, RT is effective in controlling pain and providing neurologic recovery, and it is routinely used as adjuvant therapy even after surgery.
- The most common fractionation scheme is a total of 30 Gy in 3-Gy daily fractions for 10 days.
- Stereotactic Radiosurgery (SRS) allows precise high-dose targeting, minimizing exposure of the surrounding cord.

Chemotherapy
- As in BMTS, chemotherapy has a limited role in metastatic spinal tumors.

25.9 Neoplastic Meningitis

25.9.1 Epidemiology

- Neoplastic meningitis (NM) is defined as the infiltration of subarachnoid space by neoplastic cells (Figs. 25.3 and 25.4).
- NM is detected in 4–15 % of patients with solid tumors (especially breast, lung, and melanoma), in 5–15 % of leukemias and lymphomas and in 1–2 % of patients with primary brain tumors (particularly posterior fossa tumors) [11].

25.9.2 Diagnostic Markers

- *Signs/Symptoms*
  - Supratentorial: psychiatric disturbances or cognitive impairment, seizures, motor and sensory deficits
  - Infratentorial: ataxia or gait disturbances, cranial nerve palsies often concomitant diffuse multiradicular e spinal cord signs and symptoms
- *Radiology*
  - Up to 7 % of these patients can present hydrocephalus at the time of diagnosis.
- *Cerebral spinal fluid (CSF)*
  - Elevated CSF protein and low glucose in approximately 75 and 40 % of cases, respectively.
  - In all the patients, CSF was positive for protein elevation.
  - Detection of malignant cells in the CSF is the diagnostic gold standard.

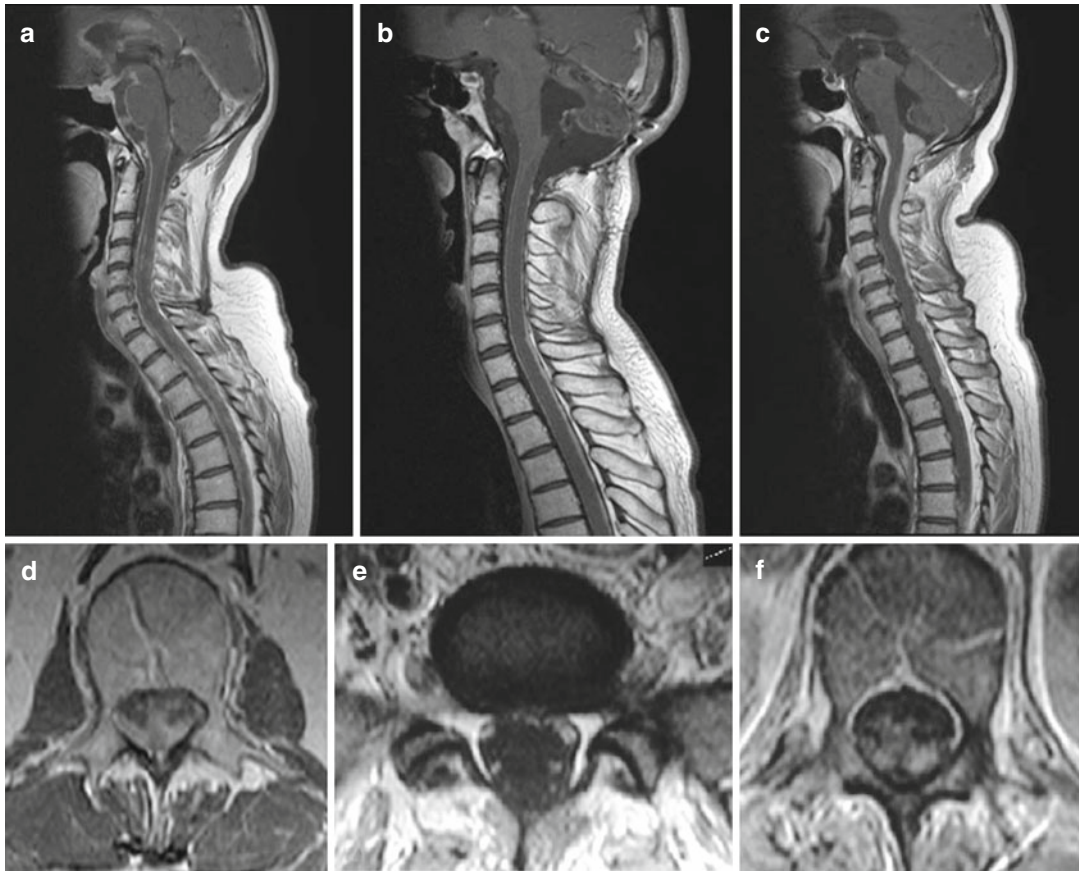

Fig. 25.4 Leptomeningeal metastases. Sagittal T1-weighted images with contrast medium, (**a**–**c**), show spread of high-grade gliomas in three different cases. Note in (**c**) the complete filling of CSF spaces by pathologic enhancement; CSF spinal dissemination of HGG implies more aggressive behavior and a worse prognosis. Axial T1-weighted images with contrast medium (**d**–**f**) demonstrate dissemination in three different cases of carcinomatosis with confluent nodular images of pathologic enhancement along the spinal roots

- Prognosis is very severe with a fatal outcome (median OS of untreated patients is 4–6 weeks).
- Negative prognostic factors are:
  - Poor performance status
  - Multiple neurologic deficits
  - Bulky CNS disease
  - CSF flow abnormalities
- Among the solid tumors, breast cancer responds best to the treatment, with median survivals of 6 months and 11–25 % 1-year.
- Standard treatment is based on high-dose systemic chemotherapy with drugs able to pass through the blood–brain barrier: methotrexate (MTX) and cytarabine, cranial or craniospinal irradiation, intrathecal administration of MTX and/or cytarabine or a depot formulation of liposomal cytarabine [11].

25.10 Primary CNS Lymphoma (PCNSL)

25.10.1 Definition and Epidemiology

- PCNSL is a highly aggressive variant of extranodal non-Hodgkin lymphoma (NHL) accounting for 1–4 % of all intracranial tumors and 1 % of lymphomas. There is an increase in incidence with advancing age, with the group over 75 years having the highest rate.

- Neither an environmental causative factor nor any other predisposing factor other than an immunocompromised status has been identified (HIV, transplanted patients, LES) [12]

25.10.2 Pathology

- Ninety percent of PCNSL are diffuse large B cell NHL lymphomas, T cell lymphomas being very rare.
- The most common locations are cerebral hemispheres, periventricular white matter, basal ganglia, and corpus callosum. Rarely, the PCNSLs affect cerebellum, brain stem, and spine cord. The lesions are solitary in 60–70 % of the cases; immunodeficient patients more frequently have multiple lesions at diagnosis.
- Ocular involvement is seen in 20–25 % of the patients at first diagnosis. Occult systemic disease has been reported in up to 8 % of patients initially thought to have PCNSL.

25.10.3 Diagnostic Markers

Clinical symptoms of PCNSL consist more frequently of cognitive dysfunction; deficits due to raised intracranial pressure, and focal symptoms affect 50 % of cases; seizures are present in a minority of patients.

Diagnostic evaluation of PCNSL routinely includes: cranial MRI (see Table 25.1); slit lamp ophthalmologic examination; CT of chest, abdomen, and pelvis; bone marrow biopsy; human immunodeficiency virus (HIV) testing; and CSF studies (flow cytometry provides an improved diagnostic sensitivity, and rarely, demonstration of clonal immunoglobulin gene arrangement can increase the yield of CFS analysis)

In PCNSL patients, a well-known finding is the impressive initial response to steroids, which occurs rapidly after the start of treatment. However, almost all patients relapse. Even if the suspicion/doubt/hypothesis of PCNSL is established by imaging, histological diagnosis of PCNSL remains mandatory.

Stereotactic biopsy is the most common approach for these patients, surgery is not considered therapeutically helpful.

Since the PCNSLs are highly sensitive to steroids, their administration before biopsy should be avoided unless in case of imminent danger of cerebral herniation.

25.10.4 Treatment and Prognosis

Radiotherapy

- PCNSL is a highly radiosensitive tumor. Present recommendations suggest whole brain radiotherapy of 45 Gy without a boost. In case of ocular involvement, the eyes are treated with 36–40 Gy.
- Whole brain radiotherapy (WBRT) achieve complete remission in 60 % of patients, but recurrence takes place approximately 1 year after RT conclusion.
- The role of radiotherapy is now questioned due to severe neurotoxicity in long-term survivors. However, a decreased dose or suppression of radiotherapy, also after intensive chemotherapy, seems to decrease progression-free survival (PFS) with a variable impact on overall survival (OS).

Chemotherapy

- Combination of chemotherapy and radiotherapy is the most effective treatment. Chemotherapy is delivered before radiotherapy (due to reduced risk of neurotoxicity), and in nonresponder patients radiotherapy rescue can be started. High dose methotrexate (HDMTX) is the drug of choice for initial treatment (3.5–8 g/m^2 iv every 10–21 days with leucovorin rescue). Response rates vary from 30 to 80 %, but a large number of responders suffer progression or relapse, with a rate of 25–55 % within a median follow-up of 13–83 months [13].
- MTX is currently combined with one or more chemotherapeutic agents, mostly high dose cytosine arabinoside (HDAraC),

with an improvement both in overall response rate and PFS in comparison to HDMTX monotherapy. But, it should be emphasized that the HDMTX + HD-AraC combination increases the frequency and severity of side effects significantly.
- Combined modality therapy using HDCHT and WBRT improve response and survival, but the crucial limitation is a significant risk of neurotoxicity (highest in patients over 60 years old).

At the end of treatment, assessment of the patient every 3 months for 2 years, then every 6 months for 3 years, and then every 12 months for 5 years is recommended.

25.10.5 Prognosis

- The International Extranodal Lymphoma Study Group (ECOG) developed a prognostic scoring system, which categorizes patients into three risk groups. In this system, five independent patient and lymphoma-related predictors were identified: age >60 years, ECOG performance status >1, increased serum LDH level, increased CSF protein concentration, and the involvement of deep regions of the brain. Patients with 0–1, 2–3, and 4–5 of these unfavorable variables had 2-year overall survival rates of 80 %, 48 %, or 15 %, respectively [12].

25.11 Meningiomas

25.11.1 Epidemiology and Pathology

Meningiomas are usually slow-growing tumors arising from arachnoid meningothelial cells that cover the brain and spine [14].

They are the most common primary intracranial tumor in adults, the annual incidence is 2.3 per 100,000, increasing with age and showing a predominance in females.

Up to 60 % of meningiomas are located in parasagittal regions, in the convexity, at the tuberculum sellae, and sphenoid ridge. Neurofibromatosis Type 2 (NF2), radiation, and head trauma are associated with an increased risk.

Meningeal lesions can be differentiated histologically into 15 subtypes and are currently categorized into 3 WHO grades; criteria include cell type, mitotic activity, cellularity, necrosis, and brain invasion.

WHO Classification	Histological features
I	Meningiomas, with low risk of recurrence and/or low risk of aggressive growth
II	Atypical meningiomas, with increased mitotic activity or (at least?) three of the following features: increased cellularity, small cells with high nucleus/cytoplasm ratio, prominent nucleoli, uninterrupted patternless or sheetlike growth, and foci of spontaneous or geographic necrosis
III	Anaplastic (malignant) meningiomas: exhibit histologic features of malignancy far in excess of the abnormalities present in atypical meningiomas

- 90 % of meningiomas are benign (WHO grade I), slow-growing lesions, 5–7 % are classified as atypical (WHO grade II) and only 3 % as malignant (WHO grade III).
- Losses on 22q12.2, encoding the tumor suppressor gene merlin, represent the most common genetic alterations in early meningioma formation. Cytogenetic studies of atypical and anaplastic meningiomas revealed gains and losses on chromosomes 9, 10, 14, and 18, with amplifications on chromosome 17.

25.11.2 Diagnostic Markers

- No signs or symptoms are specific for patients with intracranial meningiomas. Frequently, meningiomas are detected by chance ('incidentaloma')
- The most common symptom is headache (36 %) lasting for weeks to months. Other patients develop weakness or paralysis (30 %), seizures, visual field reduction, and speech problems.

- MRI is excellent for the diagnosis (Table 25.1)
- Conventional angiography is performed for preoperative endovascular embolization and is intended to minimize intraoperative blood loss.
- Meningiomas need to be differentiated with other meningeal lesions, in particular meningeal metastases from prostate, lung, kidney, or breast cancers.

25.11.3 Treatment

Surgery

- Surgery is the mainstay and standard for many patients with meningiomas; at least one third of meningiomas are not fully resected.

Radiotherapy

- Fractionated radiotherapy is efficacious with local control rates of 80–95 %. Indications for RT depend on tumor size, WHO grade, and include residual or nonresectable meningioma, recurrent or progressive tumor, and meningioma of WHO grade II and III. Because high-grade meningiomas have a high probability of recurrence even after gross total resection, postoperative high-dose RT (>54 Gy) has become the accepted standard of care for these tumors.
- Stereotactic radiosurgery (SRS) is currently used as an alternative to surgery for poorly accessible lesions, as a primary therapy for benign meningiomas or recurrent tumors, and as an adjuvant treatment after conservative resection. Local control rates following SRS are 75–100 % at 5–10 years. For atypical and malignant meningioma SRS is reserved to recurrences; the experience in this field is, however, very limited.

Chemotherapy

- Chemotherapy has a limited role, and only three drugs are recommended to treat patients with refractory and high-grade meningiomas: hydroxyurea, interferon-α 2B, and sandostatin long-acting release.

25.11.4 Prognosis

- Most meningiomas have a good prognosis; surgery and adjuvant radiotherapy are often curative. About three-quarters of grade I meningioma patients survive at least 10 years without a recurrence.
- Patients with Grade II meningiomas have a recurrence within 5 years on average; patients with Grade III tumors have a recurrence within an average of 2 years.

25.11.5 Prognostic Factors

- The extent of resection and the WHO tumor grade are the most strong prognostic factors.
- Relapse rates in WHO grade I/II/III of 7/40/80 %, respectively have been reported, and median survival was >10/11.5/2.7 years.
- Tumors that present with brain or bone invasion show poorer outcomes compared with no invading tumors.
- Meningiomas with progesterone receptors show lower recurrence rates (5 %) in comparison to tumors positive for estrogen receptors or tumors lacking sex hormone receptors (30 %).

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Neurofibromatosis Type 1 and Type 2

26

Marica Eoli

Key Facts

- **Terminology and definitions** – *NF1* and *NF2* are autosomal dominant cancer predisposition syndromes characterized by multiple tumors of the nervous system as well as lesions of the eyes and skin. In *NF1*, disorders of cardiovascular system, spine, and long bones are often present.
- **Clinical features and epidemiology** – *NF1* incidence is one in 3000 live births. *NF2* incidence is 1 in 33,000.
  NF1 – Its main clinical characteristics are multiple café-au-lait spots, axillary and inguinal freckling, and multiple cutaneous neurofibromas. *NF2* – Main characteristics are bilateral vestibular schwannomas or non-vestibular intracranial and spinal tumors.
- **Diagnostic markers** – *NF1* and *NF2* – Diagnosis is based on clinical and molecular findings.
  - **Laboratory**
    - **Genetic** – *NF1* – Caused by intragenic mutations or deletions of the NF1 gene on 17q11.2. *NF2* – Caused by intragenic mutations or deletions of tumor suppressor gene 22q12.2.
  - **Imaging** – Brain and spinal MRI are first choice.
- **Top differential diagnoses** – *NF1*: Legius syndrome. *NF1* and *NF2:* multiple meningiomatosis; schwannomatosis.
- **Prognosis**
  - **Therapy** – *NF1* and *NF2*: surgical excision of tumors, radiosurgery, radiotherapy.
  - **Disability** – *NF1* – Malignancy and vasculopathy are the most important causes of death; life expectancy is reduced by 8–15 years. Until 50 years of age, the prevalence of malignant brain tumors is up to 100 times greater than expected. *NF2* – Mean age of death is 62 years although more than 40 % of these patients die before the age of 50 years.

Abbreviations

MPSNT, malignant peripheral nerve sheath tumors; NF1, Neurofibromatosis 1/Von Recklinghausen Disease; NF2, Neurofibromatosis type 2

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26.1 Neurofibromatosis Type 1

26.1.1 Terminology and Definitions

Neurofibromatosis 1 (OMIM #162200) (NF1) (alias Von Recklinghausen Disease) is a cancer predisposition syndrome with neurocutaneous manifestations and involvement of the skin, eye, central or peripheral nervous system, cardiovascular system, spine, and long bones. Diagnosis is made based on the diagnostic criteria defined at the NIH 1987 NF consensus conference. NF1 is an autosomal dominant disease with nearly 100 % penetrance, caused by inactivating intragenic mutations or deletions of the NF1 gene (on 17q11.2) (OMIM #613113). Almost half of all affected individuals have de novo mutations (Fig. 26.1) [1].

26.1.2 Epidemiology

The incidence at birth is approximately one in 3000 individuals [2].

26.1.3 Clinical Features

A high clinical interfamilial and intrafamilial variability characterizes NF1 phenotype, and clinical manifestations develop over time. The main clinical characteristics are multiple café-au-lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, iris Lisch nodules, and learning disabilities (in at least 50 % of individuals with NF1). Less frequent features include macrocephaly, short stature, and potentially more serious manifestations such as plexiform

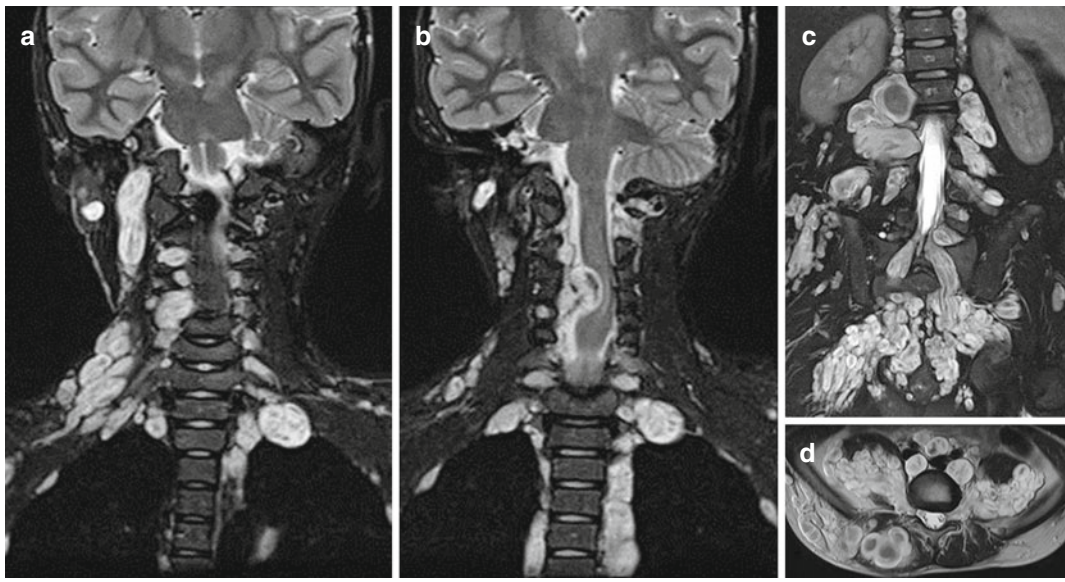

Fig. 26.1 NF1. Coronal and axial T2-weighted images (**a**–**d**) show multiple, asymmetric plexiform neurofibromas of the bilateral brachial plexuses and of bilateral lumbar plexuses. Note the confluent aspect of the tumors along the nervous trunks

neurofibromas, optic nerve and other central nervous system gliomas, malignant peripheral nerve sheath tumors, scoliosis, tibial dysplasia, and vasculopathy.

26.1.4 Diagnostic Markers

The diagnosis of NF1 is usually based on clinical findings. Molecular genetic testing of *NF1* is available.

Brain and spinal MRIs – Are useful in characterizing tumors, structural abnormalities and the brain, and signs of cerebrovascular disease.

MRI – Is the method of choice for demonstrating the size and extent of plexiform neurofibromas and for monitoring their growth over time.

26.1.5 Top Differential Diagnoses

Legius syndrome, a dominantly inherited disease caused by heterozygous pathogenic mutations of *SPRED1*, includes multiple café-au-lait spots, axillary freckling, macrocephaly and, in some individuals, facial features that resemble Noonan syndrome, but without Lisch nodules, neurofibromas, and central nervous tumors.

NF1 needs to be differentiated from Neurofibromatosis 2 (OMIM #10100) (see below) that is genetically and clinically distinct from NF1.

Schwannomatosis (OMIM # 162091) (multiple schwannomas of cranial, spinal, or peripheral nerves, usually without vestibular, ocular, or cutaneous features of NF2).

26.1.6 Prognosis

26.1.6.1 Therapy

Complications involving the eye, central or peripheral nervous system, cardiovascular system, spine, or long bones must be referred to a specialist. The treatment of plexiform neurofibromas is empiric, with surgery being the primary option for those lesions that cause a major degree of morbidity. When possible, complete surgical excision of malignant peripheral nerve sheath tumors is required. Chemotherapy of optic gliomas is generally unnecessary as they are usually asymptomatic and clinically stable. Only dystrophic scoliosis often requires surgical management [1, 2].

26.1.6.2 Prognosis

For NF1, a patient's life expectancy is reduced by 8–15 years. Malignancy (especially malignant peripheral nerve sheath tumors, MPSNT) and vasculopathy are the most important causes of early death in individuals with NF1. Tumors primarily involve the nervous system; for patients with NF1, the prevalence of malignant brain tumors is up to100 times greater than expected up to 50 years of age. Furthermore, the incidence for MPSNT is about 8–13 % among patients with NF1 while 0.001 % in the general population.

26.1.6.3 Disability

Plexiform neurofibromas are the most common and debilitating complications of NF1. They are clinically detected in 27 % of patients, and imaging reveals lesions in about 50 % of individuals with NF1. Plexiform neurofibromas are at risk for malignant transformation in MPNST [1, 2].

Optic glioma, the most common neoplasm in children, detected in about 15 % of patients, is usually asymptomatic and remains so during life,

although females are more likely than males to require treatment. The course tends to be more benign than in children without NF1 [3].

Brain stem and cerebellar gliomas in individuals with NF1 may also have a less aggressive course than in those who do not have NF1. Non-optic gliomas and malignant peripheral nerve sheath tumors within the field of treatment are substantially more common in NF1 patients with gliomas who were treated with radiotherapy [4].

26.2 Neurofibromatosis Type 2

26.2.1 Terminology and Definitions

Neurofibromatosis type 2 (OMIM #10100) (NF2) (alias bilateral acoustic neurofibromatosis) is a cancer predisposition syndrome characterized by multiple tumors of the nervous system as well as lesions of the eyes and skin.

26.2.2 Epidemiology

The actual prevalence is 1 in 60,000. The birth incidence has been approximated to 1 in 33,000 [5, 6]

26.2.3 Clinical Features

Adults in general present with symptoms related to vestibular schwannomas, whereas children more frequently present with visual disturbance, skin lesions, mononeuropathies, or symptoms related to other, non-vestibular intracranial or spinal tumors. Bilateral vestibular schwannomas are the common feature and are present in 90–95 % of patients. Hearing loss and tinnitus are the presenting symptoms in 60 % of adults and in 30 % children. Meningiomas are the second most common tumor and can be located intracranially (45–58 %) or can be spinal. More than 75 % of intramedullary spinal-cord tumors found in NF2 are ependymomas. Loss of visual acuity is often seen in patients with NF2 due to optic nerve meningiomas, cataracts, and retinal hamartomas. In adulthood, 3–10 % of patients may develop a severe polyneuropathy although up to 40 % of adults show evidence of polyneuropathy even in the absence of any neural compression by tumor. Around 70 % of patients have some skin involvement (skin plaques, subcutaneous tumors, intradermal tumors) (Fig. 26.2) [5, 6].

Diagnostic markers – Most patients can be diagnosed with NF2 at presentation based on the Manchester diagnostic criteria, but it is often difficult to confirm genetically the diagnosis in many patients due to mosaicism.

26.2.4 Diagnostic Markers

These are based on clinical criteria; the Manchester diagnostic criteria are the most widely used and include patients without a family history of this disorder or bilateral vestibular schwannoma but who have other multiple, related lesions.

NF2, caused by inactivating intragenic mutations or deletions of the NF2 tumor suppressor gene situated on chromosome 22q12, which encodes the protein merlin, is an autosomal dominant disease with nearly 100 % penetrance by 60 years of age. Almost half of all affected individuals have a de novo mutation. In de novo patients a high degree of mosaicism is present.

26.2.5 Imaging

High resolution contrast enhanced brain MRI and spinal MRI are useful in showing tumors and for monitoring their growth over time.

26.2.6 Top Differential Diagnoses

NF1. Schwannomatosis (OMIM 162091) (multiple schwannomas of cranial, spinal, or peripheral nerves, usually without vestibular, ocular, or cutaneous features of NF2).

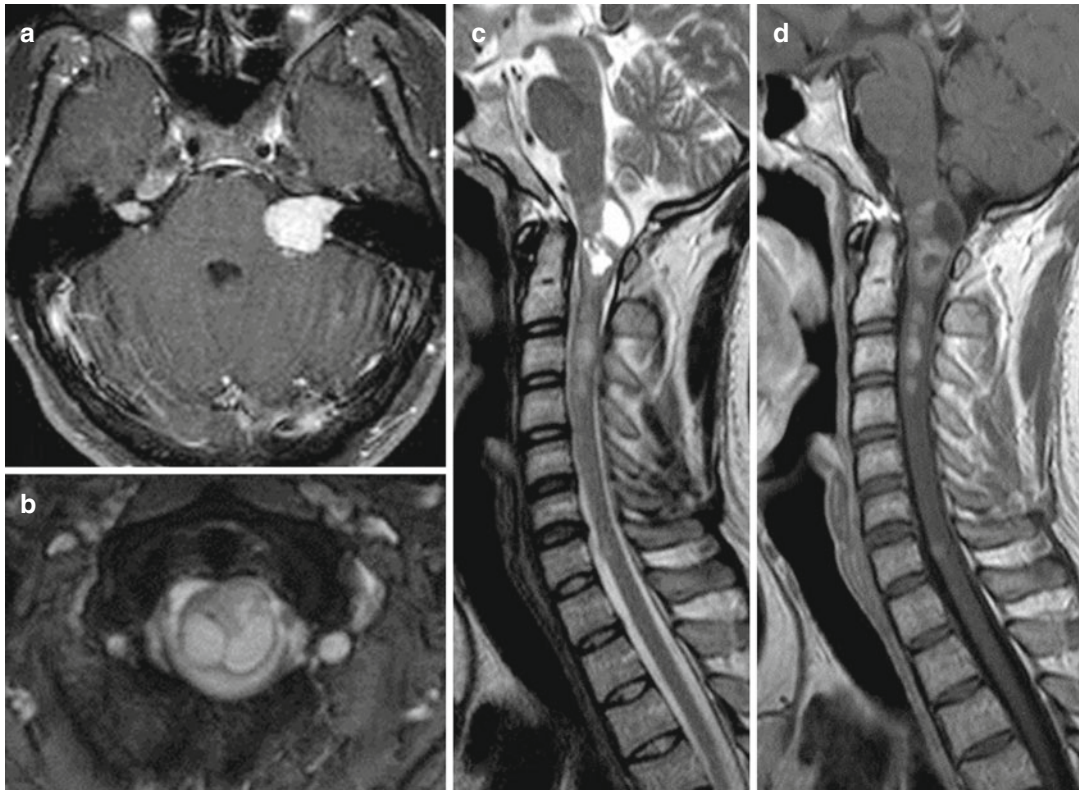

Fig. 26.2 NF2. Axial T1-weighted image after contrast medium (**a**) shows bilateral asymmetric schwannomas of both VIII cranial nerves. Axial T2- (**b**) and sagittal T2-weighted image and sagittal T1-weighted image after contrast medium (**c**, **d**) demonstrate a large intramedullary neurofibroma located in the medulla oblongata and in the cervical spinal cord that appear enlarged

Multiple meningiomatosis may overlap with NF2, but it does not manifest other NF2 features and patients have no family history of meningioma disease.

26.2.6.1 Therapy

For vestibular schwannomas, the management options include conservative management, surgical excision, and radiotherapy, usually in the form of stereotactic radiosurgery or, more recently, medical therapy. For the treatment of intracranial meningioma, surgery is the primary option for those lesions, which could cause a major degree of morbidity. Radiosurgery is less effective for the management of meningiomas than vestibular schwannomas. Spinal schwannomas and meningiomas can require excision if they are causing compressive symptoms, and approximately 30 % of NF2 patients require spinal surgery during their lifetime [5, 6].

26.2.6.2 Prognosis/Disability

In the past, two phenotypic groups were identified. Those with more aggressive disease were termed "Wishart" type. Those with milder disease were called "Gardner" type. Hearing loss and deafness, usually unilateral at time of onset, are irreversible in most patients.

The mean actuarial survival has been shown to be 62 years, although more than 40 % of these patients died before the age of 50 years. Early age at symptom onset is associated with a heightened risk of early mortality. More than 99 % of vestibular schwannomas in NF2 are benign, but they remain a substantial cause of morbidity because of their location. Due to the higher rate

of atypical or malignant meningiomas in NF2 patients, the presence of intracranial meningiomas is associated with a 2.5-foldrise in relative risk of mortality.

The average age at symptom onset in NF2 is 20 years but diagnosis is delayed on average by 7 years. The range of disease progression is highly variable, most patients become deaf and many will eventually need wheelchair assistance. According to a meta-analysis, vestibular schwannomas have highly variable growth rates that decrease inversely with age. The rate of hearing loss often differs between the ears in affected individuals [5, 6].

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Paraneoplastic Neurological Syndromes

27

Marco Zoccarato, Luigi Zuliani, and Bruno Giometto

Key Facts

- **Terminology and definition** – Diseases of the nervous system generated by the remote, nonmetastatic effect of a malignancy.
- **Clinical features** – Acute/subacute onset of focal or multifocal involvement of central, peripheral, and autonomic nervous system.
- **Diagnostic markers**
  - **Laboratory**
    - CSF with increased lymphocytes and protein, IgG intrathecal synthesis. Positivity for onconeural and neuronal surface antibodies in serum and CSF.
  - **Pathology** (variable, depending on Ab association); IgG and complement deposits, gliosis, neuronal loss, B cells and plasma cell infiltrates.
- **Top differential diagnosis** – Prion disease, infectious encephalitis, degenerative disorders, temporal lobe epilepsy, toxic and metabolic ataxia, radiculopathies, vitamin B12 deficiency, Guillain-Barré syndrome.
- **Therapy** – Steroids and immunoglobulins are efficacious in children affected by opsoclonus-myoclonus. Plasma exchange, steroids, and intravenous immunoglobulins can be very effective in *PNS associated with antibodies against surface antigens*.
- **Prognosis** – The prognosis of individual paraneoplastic neurological diseases varies considerably. In forms involving antibodies against neuronal surface antigens, tumor removal and immunosuppressive treatment can lead to complete recovery. Two years after onset, 50 % of patients with paraneoplastic encephalomyelitis, limbic encephalitis, and dysautonomia had died. Patients with sensory neuronopathy, paraneoplastic cerebellar degeneration, and Lambert-Eaton syndrome had a better prognosis, with over 50 % of patients surviving at 24 months.

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Abbreviations

ADH, antidiuretic hormone; CSF, cerebrospinal fluid; EMG, electromyography; LE, Limbic Encephalitis; LEMS, Lambert-Eaton myasthenic syndrome; OMS, Opsoclonus-myoclonus syndrome; OMS, opsoclonus-myoclonus syndrome; PCD, paraneoplastic cerebellar degeneration; PEM, paraneoplastic encephalomyelitis; PNS, paraneoplastic neurological syndromes; SCLC, small-cell lung cancer; SPS, Stiff Person Syndrome; SSN, sensory neuronopathy

27.1 Terminology and Definitions

Paraneoplastic neurological syndromes (PNS) are a group of diseases caused by nervous system impairment generated by the non-metastatic remote effect of a malignancy.

27.2 Clinical Features

Approximately one in 10,000 patients with a tumor can develop a symptomatic PNS [1]. Some forms occur more frequently, as Lambert-Eaton disease (3 % of patients affected by small-cell lung cancer [SCLC]) [2]; 50 % of patients with osteosclerotic plasmacytoma are affected by POEMS syndrome, and a growing number of cases of encephalitis associated with anti-NMDA receptor and VGKC antibodies are being reported.

The clinical characteristics of individual PNS vary according to the site involved. Nonetheless, it is helpful to specify two common characteristics:

(a) The neurological signs and symptoms have a subacute onset
(b) The neurological disease often precedes clinical evidence of the tumor

27.2.1 Classification According to Associated A ntibodies

The pathogenesis of PNS is immune mediated. The immune response causing the disease produces various types of antibodies directed against antigens located in the central or peripheral nervous system. PNS can be classified into two categories.

1. PNS associated with antibodies directed against intraneuronal antigens ectopically expressed by the tumor cells (onconeural antibodies). They accompany cancers (lung, breast, ovary, and testicular) and are characterized by poor responsiveness to tumor removal and immunomodulatory or immunosuppressive therapy. The antibodies associated with this group of PNS do not have pathogenic relevance, but are highly specific diagnostic markers.
2. The PNS associated with antibodies directed against neuronal surface antigens (e.g., NMDA- or AMPA-type glutamate receptor proteins associated with potassium channels, such as LGI1 or CASPR2, etc.) are less frequently associated with an underlying tumor but can be paraneoplastic and associated with teratomas, thymomas, and SCLC. This group differs in its greater responsiveness to treatment and typically manifests in forms of encephalitis and encephalopathy; peripheral forms have also been described: neuromyotonia and Lambert-Eaton myasthenic syndrome (LEMS).

27.2.2 Paraneoplastic Encephalomyelitis

Paraneoplastic encephalomyelitis (PEM) constitutes the paradigm of PNS. Pathologically, it is characterized by neuronal loss, microglial

proliferation, and inflammatory infiltrates with multifocal distribution. Its multiregional clinical picture can affect the hippocampus, trunk, spinal cord, or dorsal root ganglia. Involvement can also extend to the peripheral nerves and myenteric plexus, giving rise to encephalomyeloneuritis.

27.2.3 Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD) has a subacute course. Its progression often confines the patient to bed within 3 months, although symptoms can subsequently stabilize. PCD is associated with ovarian and breast cancer, SCLC, and Hodgkin's lymphoma.

27.2.4 Sensory Neuronopathy (See Chap. 35)

Sensory neuronopathy (SSN) involves the neuronal cell body in the dorsal root ganglion. It is associated with SCLC in 70–80 % of cases, but can also present during ovarian or breast cancer, sarcoma, or Hodgkin's lymphoma. The onset of SSN is subacute and rapidly progressive, stabilizing after a few weeks.

The pathological process leads to a typical asymmetric, non-length-dependent pattern of sensory nerve degeneration. Symptoms include dysesthesia and mainly deep sensory loss, with sensory ataxia. SSN affects 74 % of patients with paraneoplastic encephalomyelitis.

SSN is prevalently associated with anti-Hu antibodies.

27.2.5 Opsoclonus-Myoclonus Syndrome

Opsoclonus-myoclonus syndrome (OMS) is characterized by chaotic saccadic eye movements in all gaze directions, and is associated with ataxia and head, trunk, and limb myoclonus. Paraneoplastic forms of OMS are relatively rare, whereas idiopathic forms are more often observed in children affected by neuroblastoma or in women with breast cancer harboring anti-Ri antibodies.

27.2.6 Paraneoplastic Limbic Encephalitis Associated with Onconeural Antibodies

Paraneoplastic limbic encephalitis (PLE) is characterized by the classic triad of anterograde amnesia, seizures, and psychiatric symptoms. PLE precedes clinical evidence of malignancy by up to 4 years. Onset is acute or subacute. Seizures are present in approximately 50 % of patients [3]. Extra-limbic symptoms may also be present with sleep disorders and dysautonomia.

27.2.7 Encephalitis with Anti-VGKC Antibodies (Anti-LGI1 and Anti-CASPR2)

Anti-VGKC antibody-associated limbic encephalitis differs from classical PLE in its good response to immunomodulatory therapy and in its high proportion of nonparaneoplastic cases (up to 70–80 %). Characteristic is the frequent presence of refractory hyponatremia due to inappropriate antidiuretic hormone (ADH) syndrome.

Anti-VGKC-Ab may be specific for leucine-rich glioma inactivated protein 1 (LGI1) and contactin-associated protein-2 (CASPR2), associated with VGKC channels. Patients with anti-LGI1 antibodies present typical forms of limbic encephalitis, while those harboring anti-CASPR2 antibodies present encephalitis-like symptoms (cognitive deficits, confusion, amnestic disorders, hallucinations, seizures) associated with peripheral hyperexcitability (Morvan's syndrome) [4].

27.2.8 Encephalitis with ANTI-NMDA-Receptor Antibodies

Anti-NMDAR receptor encephalitis is probably the most frequent form of encephalitis associated with antibodies directed against surface antigens. It more frequently affects females (70–80 % of cases) of a mean age of 22–23 years and children (up to 40 % of cases).

In 70 % of cases, patients experience onset with prodromal flu-like symptoms, followed a few days later by typical manifestations of the pathology, consisting of:

(a) Psychiatric symptoms
(b) Cognitive disorders
(c) Depressed consciousness
(d) Movement disorders (orofacial dyskinesias, dystonia)
(e) Seizures
(f) Dysautonomia
(g) Hypoventilation

While the primary signs in adults are chiefly psychiatric, children more often manifest movement disorders and seizures.

27.3 Diagnostic Markers

CSF Signs of inflammation, oligoclonal bands.

Brain MRI Inflammatory lesions in the temporal region (limbic encephalitis/LE, Fig. 27.1), cerebellar atrophy (PCD).

EEG Non-specific slow disorganized or epileptic activity.

Electromyography (EMG) Non-length dependent pattern (SSN); decremental response to repetitive nerve stimulation (myasthenia) and post-tetanic potentiation of CMAP (LEMS), peripheral hyperexcitability with fibrillation, and fasciculations (neuromyotonia).

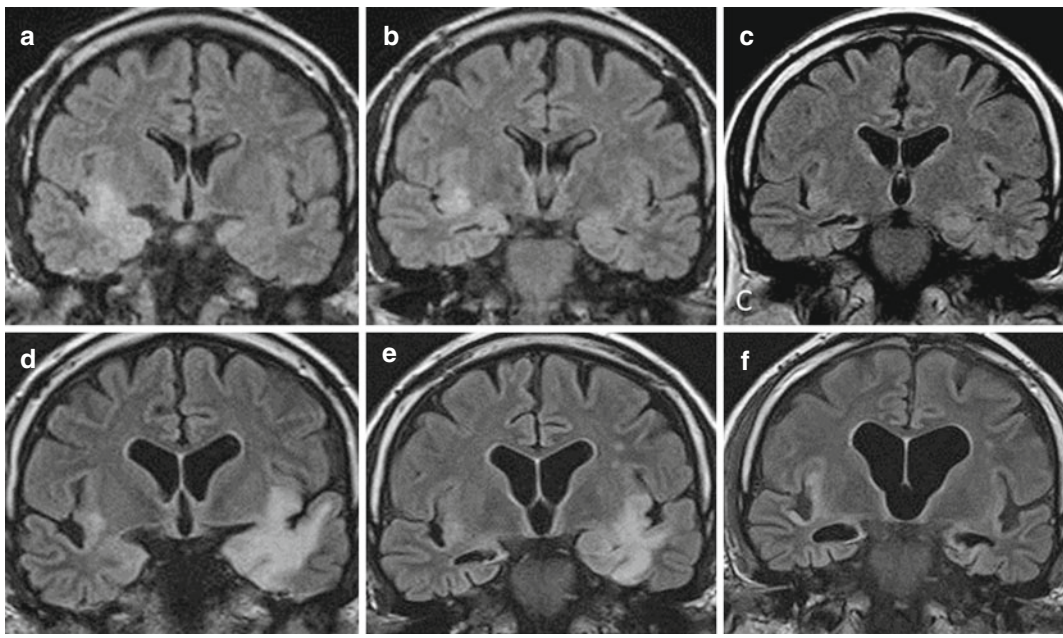

Fig. 27.1 Paraneoplastic limbic encephalitis. Coronal Flair images. (**a**, **b**) demonstrate first acute phase with swelling and hyperintensity in right insular and mesial temporal lobes; after 3 months, (**c**) atrophy is clearly observed. In (**d**, **e**) a second acute phase with swelling and hyperintensity is seen in the left temporal mesial and partially in the insular lobes. After 3 months, (**f**) bilateral marked hippocampal atrophy is present

Table 27.1 Onconeural antibodies: association with tumors and PNS

Antibody	Most commonly associated tumors	Syndrome	Antibody positivity without a tumor (%)	Frequency in tumor without PNS (%)
Anti-Hu	SCLC	Encephalomyelitis Limbic encephalitis PCD Brainstem encephalitis Intestinal pseudo-obstruction	2	16
Anti-CV2	SCLC, thymoma	Encephalomyelitis Chorea PCD Limbic encephalitis	4	9
Anti-amphiphysin	Breast, SCLC	SPS Myelopathy PEM	5	1
Anti-Ri	Breast, SCLC	Brainstem encephalitis Opsoclonus-Myoclonus	3	4
Anti-Yo	Ovary, breast	PCD	2	1
Anti-Ma2	Testicle	Limbic encephalitis Brainstem encephalitis	4	0

Table 27.2 Antibodies against surface antigens: most common association with tumors and syndromes

Antibody	Syndromes	Most commonly associated tumors	Frequency of paraneoplastic cases
Anti-LGI1	Limbic encephalitis	SCLC, thymoma	Rare
Anti-Caspr2	Limbic encephalitis, neuromyotonia, Morvan's syndrome	Thymoma	40 %
Anti-NMDAR	Encephalitis	Ovarian teratoma	6 % in children; 50 % in adults
Anti-AMPAR	Limbic encephalitis	SCLC, breast, thymoma	70 %
Anti-GABAR	Limbic encephalitis	SCLC	50 %
Anti-VGCC	LEMS	SCLC	50–60 %

Antibody Screening The antibodies are associated with clinical syndromes and tumors according to a number of common patterns (see Tables 27.1 and 27.2).

Onconeural antibodies can be detected in serum and CSF, with high concordance of results.

Tumor Screening (see Tables 27.1 and 27.2) – The search for specific tumors is guided by the clinical manifestation and, above all, the type of autoantibody [5]. In the case of limbic encephalitis, for instance, the target of cancer screening is possibly a SCLC, but also a thymoma. More rarely associated malignancies include ovarian, renal, and uterus tumors, Hodgkin's lymphoma, breast and testicular cancer, and neuroblastoma in children. Screening in cerebellar degeneration focuses on the detection of lymphoma, ovarian, breast, and lung cancers.

Opsoclonus-myoclonus: neuroblastoma, lung cancer. Lambert-Eaton: SCLC.

If oncological screening is negative, it is recommended to repeat the tests at 6-month intervals for a period of up to 4 years. This indication applies particularly to cases associated with onconeural antibodies, since the absence of a tumor is very rare in such cases.

If CT and MRI are negative, a total body PET scan should be performed.

27.4 Differential Diagnosis

In the workup of patients with suspected PNS, the differential diagnosis rules out causes producing similar clinical pictures such as, in the case of limbic encephalitis, viral encephalitis (Herpes simplex virus, HHV-6), Creutzfeldt-Jacob

disease, rapidly progressive dementia, or temporal glioma. Infectious, post-infectious, toxic, metabolic, deficiency-induced cerebellitis in the case of PCD and radiculopathy, vit. B12 deficiency, Guillain-Barré syndrome, CIDP, amyloid, hereditary, vasculitic neuropathy in case of SSN.

27.5 Prognosis

27.5.1 Principles of Treatment

Therapeutic strategies are designed to treat the cancer and control the immune response with immune modulation or immunosuppressive treatments.

27.5.1.1 Treatment of PNS Associated with Onconeural Antibodies

The efficacy of immunotherapy with steroids, plasma exchange, and intravenous immunoglobulins is very modest. The use of steroids and immunoglobulins has produced some results in children affected by opsoclonus-myoclonus. Anti-Ma2-antibody-associated encephalitis also appears to respond to treatment with high dose steroids.

The T-cell mediated mechanisms of many PNS, prompt immunosuppressive treatment with drugs such as cyclophosphamide, tacrolimus or mycophenolate mofetil, particularly in cases with worsening neurological signs and in patients with moderate-low disability (Rankin < 4).

Although immunosuppression can theoretically stimulate tumor progression, there has been no demonstration that immunosuppression is negatively correlated with the survival prognosis [6].

27.5.1.2 Treatment of PNS Associated with Antibodies Against Surface Antigens

Plasma exchange, steroids and intravenous immunoglobulins, followed or accompanied by immunosuppressive drugs can be very effective.

If first-line immunomodulation fails in forms that tend to be monophasic (but are inclined to relapse), as in anti-NMDA receptor encephalitis, it is common practice to start immunosuppressive treatment with cyclophosphamide (750 mg/m^2 per month) and/or rituximab until a clinical response is achieved. Once the acute phase is over, particularly in non-paraneoplastic cases, maintenance immunosuppression (e.g., with azathioprine or mycophenolate mofetil) for at least 1 year is an option that seems to reduce the risk of relapse [7].

27.5.2 Disability

There is undoubtedly a high degree of disability among patients with PNS since the rapid evolution of the pathology and the neuropathological mechanism of neuronal destruction mean that the best result treatment can offer is rapid control of the malignancy, which may help stabilize the neurological picture. Only symptomatic treatment approaches can slightly attenuate symptoms or slightly improve mobility.

The scenario changes in forms involving antibodies against neuronal surface antigens since tumor removal or early immunosuppressive treatment can lead to total symptom remission and thus complete recovery from the disease.

However, there are conditions, such as encephalitis associated with LGI1, in which 20–30 % of cases do not respond to treatment or forms associated with AMPAR and GABAb. These patients may present residual drug-resistant seizures and require continuous adjustments to the pharmacological therapy.

Lastly, there is a 20 % risk of recurrence in patients with anti-NMDA-receptor encephalitis and in patients with LGI1 antibodies. The recommendation in these cases is to slowly and gradually suspend immunosuppressive treatment and, in the case of recurrence, to consider the option of second-line immunosuppression.

27.5.3 Prognosis

Oncologically, however, it has been demonstrated that in the presence of paraneoplastic neurological disease, the tumor has a much less aggressive

course and therefore a better prognosis. Only rarely does the tumor present distant metastases, tending to remain localized or to invade solely into the regional lymph nodes. Ninety percent of these patients present limited oncological disease at the time of diagnosis compared to 50–60 % of patients with breast cancer and 25 % with an ovarian tumor.

Analysis of European database data has confirmed that two-thirds of patients with paraneoplastic disease presented no evidence of malignancy at the time of neurological diagnosis. Diagnosis was the result of careful, targeted diagnostic work-up and in many cases came after 3 years of follow up. The neurologist is, therefore, the first specialist with whom these patients should come into contact.

The prognosis of individual paraneoplastic neurological diseases varies considerably. Data from the said database have revealed that 2 years after onset of the neurological disease, over 50 % of patients with paraneoplastic encephalomyelitis, limbic encephalitis, and dysautonomia had died, in the majority of cases due to progression of the neurological disease. Conversely, patients with sensory neuronopathy, paraneoplastic cerebellar degeneration, and Lambert-Eaton syndrome (see Chap. 37) had a better prognosis, with over 50 % of patients surviving at 24 months, despite the presence of comparable oncological diseases in the two groups.

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Extrapyramidal Diseases: Parkinson's Disease

28

Filippo Tamma

Key Facts

- **Definitions and clinical features** – PD is a movement disorder characterized by asymmetric tremor, bradykinesia, rigidity, and postural instability
- **Diagnosis** – Clinical findings, including good and sustained response to levodopa
  - **Laboratory**
    - **Genetics** – More than 15 AD and AR genes have been associated with PD
  - **Imaging** – SPECT with DaT-scan may contribute to diagnosis
- **Top Differential Diagnoses** – Essential tremor; degenerative, vascular, toxic parkinsonisms; normal pressure hydrocephalus
- **Prognosis**
  - **Principles of treatment** – Levodopa is the golden standard in PD treatment. Deep brain stimulation of the subthalamic nucleus can improve PD.
  - **Disability** – May differ in the many phenotypic subtypes of PD. Cumulative *general surveys indicate that* 30 % of patients would lose their job within 1 year, and most after 5 years of disease. Cognitive impairment predicts more severe motor impairment and disability.

Abbreviations

AD, autosomal dominant; AR, autosomal recessive; CBD, Cortico-basal degeneration; GBA, Glucocerebrosidase; LBD, Lewy body dementia; MMSE, Mini Mental State Examination; MSA, multiple system atrophy; PAF, pure autonomic failure; PIGD, postural instability/gait difficulty; PD, Parkinson's disease; PSP, progressive supernuclear palsy; QoL, Quality of life; RBD, REM-sleep behavior disorders; SMR, Standardized mortality ratio; DBS, Deep brain stimulation; STN, Subthalamic nucleus; UPDRS-ME Unified Parkinson's Disease Rating Scale-Motor Examination

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28.1 Definition and Clinical Features

Parkinson's disease (PD) is a common neurodegenerative condition that usually presents with asymmetric tremor, bradykinesia, rigidity, and postural instability. A range of nonmotor symptoms – sleep and mood disorders, constipation, and smell alteration – may precede, even by decades, the onset of PD. The efficacy of the treatment changes over years due to the progressive nature of disease course, leading to the advanced phase of the disease.

28.2 Diagnosis

A good to excellent response to levodopa has a diagnostic value (*ex juvantibus* diagnosis).

28.3 Epidemiology

PD prevalence, second among neurodegenerative diseases, rises with age; it is more common in males than in females and in developed countries affects around 2 % of the population over 65.

Genetics Although more than 15 identified genes and genetic loci have been associated with PD, they are responsible for only a small percentage of cases. However, exposure to environmental toxicants is associated with an increased risk for PD in several epidemiological studies. A potential role for gene–environment interaction is claimed to explain PD etiology.

Imaging Imaging is not informative, apart from SPECT with DaT scan that may contribute to differential diagnosis in selected cases.

28.4 Top Differential Diagnosis

Essential tremor; Parkinsonisms; vascular, toxic, and drug-induced parkinsonism; normal pressure hydrocephalus

28.5 Therapy

After 50 years from its introduction, levodopa is still the golden standard therapy in PD treatment, simply because it is the best physiological substitute for the lacking substance. The association between levodopa and dopamine-agonists may add efficacy and reduce side effects of both. IMAO-B and I-COMT have an ancillary role (e.g., in enhancing levodopa efficacy). Interventional therapies are indicated in the advanced phase of the disease.

28.6 Prognosis

General surveys demonstrated that about 30 % of patients affected by Parkinson would lose their jobs within 1 year, and most after 5 years of disease. Moreover, the annual risk of hospitalization of Parkinson was more than 30 % [1], and PD patients had a greater risk of death than those without PD [2].

Clinical worsening of PD could be the result of two distinct processes:

1. The progression of levodopa-responsive symptoms, are associated with the degeneration of the nigrostriatal dopaminergic neurons. In PD, the age at onset of this process and its rate of progression are highly variable.
2. The evolution of levodopa-nonresponsive symptoms (the so-called axial symptoms: gait, balance, dysarthria, dysphagia), which

are caused by widespread degeneration of extranigrostriatal systems: these symptoms have a more homogeneous rate of progression and precede death by 3 to 5 years [3].

Apart from different pathological entities, which may be clustered under the definition of parkinsonisms (MSA, PSP, CBD, LBD), a wide range of phenotypic subtypes that differ in clinical features, response to therapy, prognosis, and pathology, characterizes PD. Consequently, the analysis of PD prognosis must include this clinical heterogeneity.

Several studies have addressed this issue, but only a qualitative synthesis of the prognostic factors is possible because formal meta-analysis to aggregate quantitatively progression scores of motor impairment, disability, and quality of life (QoL) is hampered by the wide variety of outcome measures used and heterogeneity of study population.

28.6.1 Genetic Factors

Genetically determined forms of PD are characterized by a wide clinical variation even among members of the same family. However, it is possible to indicate some general trends. Homozygous or compound heterozygous mutations in three genes (parkin, PINK1, DJ-1) can cause autosomal recessive forms of early-onset parkinsonism with a slower and more benign course and usually without atypical signs nor cognitive involvement. In the autosomal dominant forms there is a wider variability of the clinical course: patients with alpha-synuclein mutation (in particular the missense mutations) have a more severe course; patients carrying the LRKK2 mutations present with a clinical heterogeneity, and those with the most common mutation (G2019S) show a typical course which resembles the classical form. Parkinsonism associated with the GBA mutation is characterized by cognitive comorbidity or a typical Lewy body dementia [4].

28.6.2 Gender

The annual progression rate of both motor impairment and decline in QoL was slower in women [5], and male gender was associated with an increased progression of motor impairment [3], while survival rate appeared to be comparable both in men and in women with PD [6].

28.6.3 Clinical Factors

Age at Onset The increment of motor impairment seems to be greater in patients with older age at onset (≥78 years) after comparable disease duration of approximately 5 years [7]. A similar observation confirmed that patients with an older age at onset (>57 years) had a more rapid progression in freezing and in parts I and II of UPDRS (mentation and activities of daily living). Older age at onset has been associated with a higher worsening in UPDRS-ME and Hoehn & Yahr scales, as well as, in an incident study, with worse progression of motor impairment, disability, and quality of life [5].

Clinical Phenotype "Postural instability/gait difficulty" (PIGD) phenotype is one of the main prognostic factors, and the PIGD group has a more rapid annual rate of decline in UPDRS score compared to the tremor-dominant group. On the other hand, it has been shown that a large proportion of patients may convert from the

tremor-dominant to the PIGD-dominant subtype over an 8-year follow-up [8]. Symmetrical disease and older age at onset are predictors for faster progression to the onset of balance disorder. The time course of disease status based on UPDRS is a better predictor of the occurrence of future clinical events like death, disability, cognitive impairment, and depression than any baseline disease characteristics [9].

Magnitude of Levodopa Response A poor response to levodopa was a significant predictor of increased mortality (independent of disease severity and of levodopa dosage) in a study conducted in the DATATOP cohort after a 13-year follow-up [10].

Cognitive Dysfunction Cognitive impairment at baseline predicted more severe motor impairment and disability in a population-based study. Presence of dementia, together with older age at onset and unresponsiveness to dopaminergics has been associated with early nursing home placement.

Cognitive decline appears to be delayed in younger age-at-onset patients but once it began, it occurred at a similar degree in both groups. A baseline MMSE < 29 was a significant risk factor for incident dementia [11].

The risk of death is strongly related to the presence of dementia, with a threefold increase in the standardized mortality ratio (SMR). Survival, life expectancy (LE), and anticipated age at the time of death (AAD) in patients with PD are much lower compared with the general population, apart from those who do not develop dementia, who appear to be near norm for population mortalities [12].

REM-sleep Behavior Disorders RBD may precede the onset of neurodegenerative diseases up to some decades. Most individuals with isolated RBD will develop a Lewy body disorder (PD, DLB, MSA) with time [13], if they live long enough. At the same time, in a population-based cohort study, individuals with isolated RBD developed mild cognitive impairment and PD [14] or DLB. Moreover, a relevant association between RBD and the development of dementia has been shown in PD patients [15].

Psychiatric Symptoms Depression has not been frequently studied as a determinant of prognosis in PD. A greater progression of motor impairment and cognitive decline (3 points decline versus 1 point decline in MMSE, $p < 0.05$) was found in PD patients with major depression compared with both minor and no depression patients, after a 12-month follow-up [16]. A more recent study shows that psychiatric and other nonmotor symptoms contribute significantly to disability in PD [17]. Apathy at baseline may predict a worse performance in cognitive tests (particularly visuospatial and frontal tests) at a 2-year follow-up.

Neurogenic Orthostatic Hypotension When associated with neurodegenerative diseases, NOH is responsible of an increased risk of mortality with respect to general population (see chapter 36). PD patients result to have an intermediate prognosis between PAF and MSA patients [18].

28.6.4 Allied Therapies

There is good evidence that exercise is effective in improving motor performance in Parkinson's disease. Recent studies show that intensive exercise may promote cell proliferation and neuronal differentiation in animal models. It is postulated that the motor improvement achieved in PD patients through intensive rehabilitation strategies may have a relation with similar neuroplastic effects and slow down disease progression [19].

28.6.5 Socioeconomic Issues and Caregiver Role

Racial and socioeconomic factors may influence the prognosis of Parkinson's disease. In particular, a lower socioeconomic status may negatively affect disease severity and disability because of

problems in diagnosis, access to care, physician referrals, and patient attitudes regarding the appropriate threshold for seeking treatment at a specialized centre [20]. Caregivers are heavily involved in the management of patients and their role may influence the disease burden and eventually the prognosis. Even if no formal data are reported in the literature, expert opinion suggests that PD patients with similar disease course and severity might experience different levels of quality of life and, eventually, length of survival, depending on how wise and equilibrated the approach to the disease provided by their caregivers is.

28.6.6 Influence of Therapy on the Course of the Disease

The possibility to favorably influence the progression of PD, and consequently its prognosis, with a pharmacological agent is still a matter of debate.

In the last decades, many substances have been endorsed for their having disease-modifying properties, but none of them has shown an unequivocal ability to slow down or ameliorate the underlying neurodegenerative process or improve prognosis.

On the other hand, no evidence supports the role of levodopa therapy in accelerating the progression of PD [21]; moreover, there is some evidence that it can hamper the progression of disease in comparison to placebo.

Dopamine agonists (both ergot and nonergot ones) in studies of direct comparison with levodopa seemed to reduce the disease progression, but critical analysis of such studies casts some doubts on the real relevance of the results.

IMAO-B (selegiline and the more recent rasagiline) in well-designed clinical trials, apparently slow down the progression of the disease, but the clinical significance and the magnitude of the real impact on quality of life of patients seem trivial.

Surgery – Deep brain stimulation of the subthalamic nucleus (STN-DBS) can dramatically improve the control of both parkinsonian symptoms and complications in the advanced stages of PD. Some animal studies [22] and many clinical observations of an apparent arrest of clinical progression after STN-DBS seem to acknowledge a role for this technique to favorably influence the disease progression. At the same time, the lack of case–control studies and the inexorable progression of axial symptoms and cognitive decline [23] suggest a cautious attitude while awaiting more robust studies.

In conclusion, Neurologists should be able to properly utilize all the available strategies to treat dopaminergic symptoms (drugs, continuous infusions, surgery). On the other hand, being not available drugs to treat levodopa-non responsive symptoms, and lacking effective disease-modifying agents, neurologists must consider all those allied therapies and strategies which are less literature supported (and commercially sponsored) but can positively influence the quality of life of patients and their families and eventually the prognosis.

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Extrapyramidal Diseases: Atypical Parkinsonisms

29

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Key Facts

- **Terminology and definitions**
- Parkinsonisms are a heterogeneous spectrum of movement disorders, having as shared core a severe impairment of motor programming skills.
- **Clinical features**
- Rigidity and bradykinesia develop more aggressively in atypical parkinsonisms than idiopathic PD. Non-motor symptoms with early deterioration of global performances characterize these syndromes.
  - **PSP** – Prevalence 6/100,000. Onset ~66 years with gaze palsy, abrupt falls, bradykinesia, proximal and axial rigidity.
  - **MSA** – Prevalence 4.4/100,000. Onset ~55–65 years with autonomic failure, parkinsonism, pyramidal signs, and/or cerebellar ataxia.
  - **CBD** – Prevalence 4.9/100,000. Onset ~64 years with asymmetrical parkinsonism, apraxia, and psyco-cognitive dysfunction.
- **Diagnostic markers**
  - **Genetics** – Sporadic. Exceptionally, autosomal dominant transmission (PSP, CBD).
  - **Imaging** – Usually nonspecific. MRI: midbrain tectum atrophy (PSP). Sporadically, "hot cross bun sign" at MRI and/or normal cardiac uptake of [123I]MIBG (MSA), unlike PD. Asymmetrical cortical and cerebral peduncle atrophy (CBD).
- **Top differential diagnoses**
- Parkinson Disease; Lewy Body Disease; Alzheimer Disease, especially in its "Lewy Body" variant; Psychosis.
- **Prognosis**
- Range 5–10 years from clinical onset.
  - **Principles of treatment** – No effective treatments for PSP, MSA, CBD. Unstained/absent response to levodopa.
  - **Disability** – Chronic progressive (PSP; MSA, CBD).

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Abbreviations

AD, Alzheimer dementia; CBD, Cortical-Basal degeneration; LBD, Lewy Body Disease; MRI, Magnetic Resonance Imaging; MSA, Multiple System Atrophy; OPCA, OlivoPontoCerebellar Atrophy; PD, Parkinson Disease; PSP, Progressive Supranuclear Palsy; SDS, Shy-Drager Syndrome; SND, StrioNigral Degeneration; CNS, Central Nervous System

Key Facts

Parkinsonism configures the clinical prototype of a large and heterogeneous set of movement disorders, having as shared core a remarkable impairment of motor programming skills. Basal nuclei are primarily involved in the pathogenesis of parkinsonisms.

Atypical parkinsonisms are a various group of neurological syndromes where the rigidity and bradykinesia develop more quickly and aggressively than idiopathic Parkinson disease. The emergence of non-motor symptoms with early and significant deterioration of the global patient performances accounts for the poor prognosis characterizes these unusual neurological syndromes.

29.1 Progressive Supranuclear Palsy (PSP)

29.1.1 Definition

Synonym: *Steele-Richardson-Olzewski Syndrome*.

Later adult life tauopathy, characterized by severe progressive parkinsonism and by slowly progressive dementing syndrome.

29.1.2 Demographics

PSP appears to favor no racial, ethnic, geographical, or occupational group and it affects both genders, despite a slight male predominance. Average age at onset is 66 years, although earlier onset may occur. Approximately, 6 people per 100,000 population have PSP [1].

29.1.3 Clinical Features

PSP is chronically progressive syndrome usually beginning in the sixth decade with some combination of difficulty in balance, ocular and visual disturbances, abrupt falls, garbled speech, and dysphagia [2]. The most ordinary early complaint is unsteadiness of gait and unexplained backwards falling. The gaze palsy is generally downward. Doll's eye sign is normal, denoting the supranuclear topography of the disorder.

Other features are facial hypomimia, bradyphrenia, frontal type dementia with impairment of executive functions, mood disorder with changes of personality. Unlike Parkinson disease (PD), PSP seldom produces tremor; besides, rigidity is classically axial, with relative saving of the limbs [3].

29.1.4 Pathology

PSP is a sporadic tauopathy that presents neurofibrillary tangles in neurons and glia in specific basal nuclei, brainstem, and neocortical areas. The etiology of PSP is unknown [4].

29.1.5 Diagnosis

PSP suspected diagnosis is clinical. National Institute for Neurological Diseases and Stroke-Society for PSP (NINDS-SPSP) proposed clinical criteria to diagnose PSP [5].

29.1.5.1 Imaging

MRI has an ancillary role, especially useful in the differential diagnosis.

The atrophy of the midbrain tectum, seldom with peculiar "penguin configuration" and volumetric conservation of the pons are the main neuroradiological signs of PSP [6].

Genetics

PSP is a sporadic neurodegenerative syndrome. However, rare familial clusters have been described in which the pattern of inheritance is compatible with autosomal dominant transmission [7].

29.1.6 Top Differential Diagnoses

Parkinson Disease; Multiple System Atrophy; Cortical-Basal Syndrome; Lewy Body Disease; Alzheimer dementia (AD-LBD variant).

29.1.7 Therapy

Currently, there are no effective treatments for PSP.

Only a few patients respond to dopaminergic drugs; however, pharmacological responsiveness often is short-lived and incomplete [8].

29.1.8 Prognosis

There are two main clinical subtypes in PSP:

1. Richardson's syndrome (RS): prominent postural instability, supranuclear vertical gaze palsy and frontal dysfunction.
2. PSP-Parkinsonism (PSP-P): asymmetrical onset, tremor, and dim initial therapeutic response to levodopa.

Walking and stability problems are commonly premature features of the disease. Visual and oculomotor deficit tend to occur early as well. Late in the course of the pathology, all these symptoms advance. Therefore, the walking becomes very problematic, if not impossible; eye movement problems get to be more disabling; finally, cognitive injury progresses to dementia.

Disease time course oscillates from 5 to 10 years after onset, with a median survival of approximately 6 years. RS patients seem to have an analogues age at syndrome onset but more quick disease evolution than patients with PSP-P. Individuals with RS show recurrent falls and develop wheelchair dependency earlier than those with PSP-P [9].

Generally, death in PSP is due to pneumonia or other internistic diseases [10].

29.2 Multisystem Atrophy (MSA)

29.2.1 Definition

Synonyms: *Striato-Nigral Degeneration*; *Olivo-Ponto-Cerebellar Atrophy*; *Shy-Drager Syndrome*.

MSA is a sporadic, rare, late onset alpha-synucleinopathy, which erupts with selective damage of definite CNS nuclei and long neural pathways.

29.2.2 Demographics

The prevalence of MSA is roughly 4.4 per 100,000 [1].

Around 55 % of cases occur in men, with typical age of onset in the late 50s to early 60s [11].

29.2.3 Clinical Features

MSA is a sporadic and rapidly progressive neurodegenerative disorder where levodopa-refractory parkinsonism is usually combined with autonomic failure, pyramidal signs, cerebellar ataxia, REM sleep behavior disorders and neuropsychiatric features. Cognitive function is relatively well preserved [11].

Formerly, MSA was considered a tripartite nosological entity: In fact, at first it encompassed strionigral degeneration (SND),

olivopontocerebellar atrophy (OPCA) and Shy-Drager syndrome (SDS). However, recently all these pathological variants were merged in two new diagnostic categories: MSA-P and MSA-C, depending on the predominant motor presentation at the time of examination [12]. In particular, MSA-P refers to a parkinsonism prevailing phenotype; MSA-C, instead, refers to a ruling cerebellar phenotype [13].

29.2.4 Pathology

MSA is a rare neurological syndrome, which presents neural and glial inclusions of alpha-synuclein (*Papp-Lantos bodies*) with rapid progression and currently poor therapeutic management [14]. MSA etiology is unknown.

29.2.5 Diagnosis

For consensus criteria to diagnose MSA, please see the medical review of Gilman et al. [15].

29.2.5.1 Imaging

There is no definitive brain imaging study for diagnostic purpose of MSA. Sporadically, the "hot cross bun sign" is seen on transverse T2-weighted magnetic resonance images of the brain as a cruciform hyperintensity in the pons Varolii [16].

In the case of diagnostic doubt, cardiac uptake of [123I]MIBG separates Parkinson Disease (PD)/Lewy Body Disease (LBD) from Multiple System Atrophy (MSA) [17].

29.2.6 Top Differential Diagnoses

Parkinson Disease; Progressive Supranuclear Palsy; Cortical-Basal Syndrome; Lewy Body Disease; Psychosis.

29.2.7 Therapy

Currently, there is no cure for MSA, so treatment focuses on managing the signs and symptoms (see Chap. 36). In some individuals, levodopa may improve motor function; however, the benefit may not continue as the disease progresses.

29.2.8 Prognosis

No different survival has been established between MSA-P and MSA-C; however, MSA-P patients had more quick functional decline than MSA-C patients. The average time from preliminary symptoms to combined autonomic and motor impairment was 2 years (range 1 ± 10). Patients showing motor and autonomic disablement within 3 years from disease onset had a worse prognosis.

Assisted walking devices and wheelchair use took place after a median time of 3 and 5 years respectively, from onset of the disease. Patients were confined to bed or dead, after a median time of 8 and 9 years. Individuals with originally motor symptoms had enhanced risk of aid-requiring walking and need to a wheelchair compared with those primarily lamenting of autonomic symptomatology [18].

MSA time course is chronically progressive. The poor prognosis of the disease is associated not only to the motor symptoms, but especially to autonomic failure (see Chap. 36), that typically comprises urogenital dysfunction and orthostatic hypotension.

Pneumonia or other internistic complications habitually cause death in MSA. The median survival is about 8 years in MSA patients [19].

29.3 Cortical-Basal Degeneration (CBD)

29.3.1 Definition

Synonyms: *Cortico-Dentato-Nigral Degeneration with neuronal achromasia*; *Cortico-Nigral Degeneration*; *Cortico-Basal Ganglionic Degeneration*.

CBD is a sporadic, rare, progressive neurodegenerative syndrome, that typically presents with asymmetrical parkinsonism, apraxia, and psycocognitive dysfunction.

29.3.2 Demographics

The mean age of onset in CBD is 64 years. Female and male are equally affected.

Exact incidence and prevalence are unknown. Approximately, in USA its prevalence has been estimated at 4.9 per 100,000 [10].

29.3.3 Clinical Features

Signs of corticospinal disease and apraxia combined with progressive asymmetrical extrapyramidal rigidity constitute the crucial clinical abnormalities. The parkinsonism is generally unresponsive to L-dopa. Symptoms characteristically begin in one limb, with no apparent preference for the left or right side. Patients describe their limb as "clumsy," "stiff," or "dead." Sometimes, the limb adopts a dystonic posture. Ideomotor apraxia and cognitive impairment are common. "Alien-limb phenomena" with intermanual conflict appears in 50 %. Rest tremor is infrequent, but if present is usually swifter and more uneven than in PD [20].

29.3.4 Pathology

Asymmetric parietofrontal or frontotemporal cortical atrophy and pallor of the substantia nigra are the peculiar macroscopic pathologic findings.

The definition "cortico-basal degeneration" (CBD) refers to those cases which have a particular type of tauopathy at autopsy [21]. CBD etiology is unknown.

29.3.5 Diagnosis

For the clinical criteria to diagnose CBD, please see the following source [22].

29.3.5.1 Genetic

In rare familial clusters, the pattern of inheritance is compatible with autosomal dominant transmission [23].

29.3.5.2 Imaging

There is no diagnostic test. The most frequent MRI feature described in CBD is asymmetrical cortical and cerebral peduncle atrophy, usually contralateral to the clinically more seriously affected side [24].

29.3.6 Top Differential Diagnoses

Parkinson Disease; Progressive Supranuclear Palsy; Multiple System Atrophy; Fronto-Temporal Dementia; Lewy Body Disease; Psychosis.

29.3.7 Therapy

Treatment options remain limited and mostly address symptoms.

Levodopa response is often absent or moderate.

29.3.8 Prognosis

The prognosis is poor with death occurring nearly within 10 years of diagnosis [25].

Death in CBD is typically a consequence of pneumonia or other medical complications, such as sepsis or pulmonary embolism.

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Extrapyramidal Diseases: Huntington's Disease

30

Franco Valzania

Key Facts

- **Definitions** – Huntington's disease (HD) is an autosomal dominant neurodegenerative movement disorder.
- **Demographic** – Prevalence 0.2–10/100,000 with a geographical gradient from south to north.
- **Clinical feature** – Progressive condition characterized by involuntary "choreic" movements, cognitive deficit, and psychiatric features.
- **Pathogenesis** – Expansion of a CAG sequence in the coding region of the huntingtin (Htt) gene in exon 1 of 4p16.3 chromosome.
- **Diagnostic Markers**
  - **Genetics** – CAG trinucleotide repeats in chromosome 4p16.3 ≥ 36 (normal < 36).
  - **Imaging** – TC and MRI scans show progressive striatal atrophy, which can precede motor symptoms. Late generalized cerebral atrophy. FDG-PET: selective striatal hypometabolism even preceding of years hypotrophy at MRI.
  - **Neurophysiology** – Polygraphic recording of multiple brief muscle contractions not related to EEG activity. Reduced corticospinal excitability on TMS study.
- **Top differential diagnoses** – Dentato-rubro-pallido-luysian atrophy, ataxia telangiectasia, SCA17, neuroacanthocitosys; benign familial, Sydenham's and drug-induced, immuno-mediated chorea.
- **Therapy** – No disease-modifying treatments; symptomatic treatment of choreic movements is based on neuroleptics, benzodiazepines, and tetrabenazine. Conventional therapy for psychiatric disorders.
- **Prognosis** – Invariably fatal outcome. Mean survival 15–20 years.

Abbreviations

CAGn, number (n) of trinucleotide repeats; HD, Huntington's disease; Htt, huntingtin; TMS, transcranial magnetic stimulation; Unified Huntington's Disease Rating Scale, UHDRS.

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30.1 Definition and Clinical Features

Huntington's disease (HD) (synonym chorea major) is an autosomal dominant neurodegenerative disease characterized by involuntary "choreic" movements, with cognitive deficit and psychiatric features. It is caused by the expansion of a CAG sequence in the coding region of the huntingtin gene (IT15) located in the short arm of chromosome 4, in its N-terminal part [1].

30.2 Epidemiology

The prevalence varies in relation to the geographic region with highest incidence (5–10 cases per 100,000 inhabitants) in North America, central and northern Europe, and Oceania; 2–5 cases/100,000 in southern Europe, Asia, and South Africa; and <1:100,000 in North Africa [2].

HD more often begins in the fourth or fifth decade but can occur at any time, from the first year of age (" juvenile variant"), even up to the eighth decade ("late-onset chorea"). CAGn repeats influences the age of clinical debut with an inverse relationship with the age of onset [3]. Earlier onset in successive generations (*anticipation*) is known to be attributable to increasing lengths of the CAG repeat sequence.

30.3 Clinical Features

In the years immediately preceding the diagnosis, some behavioral, cognitive or motor changes may occur but could be so mild as to remain undetected by the same subject or family [4].

At the diagnostic stage of Huntington's disease, a typical triad of symptoms characterized by motor disorders, behavioral and cognitive deficits of subcortical type is evident [5]. Choreic movements are the marker of the disease and are observed in two thirds of cases, often combined with motor incoordination and persistence.

Chorea tends to worsen over time until a plateau, after which abnormal movements can decrease at the onset of dystonia and rigidity, typical of later and final phases. Only in juvenile cases (variant of Westfall), rigidity and dystonia are observed from the beginning.

Dysautonomic symptoms and metabolism changes can be present.

Typical cognitive impairment consists of disturbances in attention, executive functioning, and anterograde memory.

Psychiatric and behavioral disorders are present at onset in a third of cases. The suicide rate is notable (1–5 %).

Dementia is generally more severe in cases of early onset (15–40 years) than in those of later onset (55–60 years).

30.4 Diagnostic Markers

Genetics The mutation at the origin of the disease is an increase in the number of repetitions of the trinucleotide CAG (CAGn) in the first exon of the gene IT15 (7E); it encodes a protein, Htt, and the mutation implies an extension of its polyglutamine tract (poliQ). Htt plays an anti-apoptotic and neuroprotective role, regulates gene expression, axonal transport, and synaptic transmission. The allele of the IT15 gene is considered normal by 6–35 CAG repeats and pathological from 36 to 121. Individuals with 36–39 triplets may eventually manifest the disease, but it tends to be late in onset and mild in degree or limited to the senile chorea; those with more than 42 almost invariably acquire the signs of disease if they live long enough.

CT and MRI scans show progressive striatal atrophy that can precede the appearance of motor symptoms. Gross atrophy of the head of the caudate nucleus ("butterfly" appearance) and putamen bilaterally is the characteristic abnormality in symptomatic patients, usually accompanied by a moderate and later degree of gyral atrophy in the frontal and temporal regions.

FDG-PET can show selective striatal hypometabolism even several years prior to the emergence of hypotrophy as seen by conventional MRI.

Neurophysiological Study Polygraphic recording allows differentiating choreic movements from myoclonus or tics and excluding the cortical origin. Transcranial magnetic stimulation (TMS) studies reported nonspecific reduced corticospinal excitability.

30.5 Therapy

No disease-modifying treatments are available.

Symptomatic treatment of choreic movements is based on neuroleptics (preferring atypical agents and dopamine-depleting agents – mainly tetrabenazine), on overseeing the occurrence of depression, hypotension, and parkinsonism. Benzodiazepines or baclofen are employed in case of rigidity. For psychiatric disorders, conventional therapy is recommended. Supportive therapy and genetic counseling are essential.

30.6 Prognosis

HD pursues a steadily progressive course and death occurs on average 15–20 years after onset.

30.6.1 Role of the Genetic Defect as a Prognostic Factor

- *Omo-heterozygous:* homozygotes may have more parkinsonian and psychiatric symptoms and a faster evolution.
- *CAGn vs age of onset:* the number of triplets seems to be the main factor determining the time of clinical debut with an inverse relationship: the more repeats, the earlier the HD onset. This element, prognostically relevant at the time of clinical diagnosis, plays a special role in positive, pre-symptomatic genetic testing. In fact, in addition to confirming that the subject is a carrier of HD, it can allow an approximate prediction of symptoms occurrence. Usually patients with CAGn > 50 anticipate onset by about 8–10 years compared to those with CAGn < 40.
- *Paternal/maternal inheritance vs CAGn:* The paternal transmission is accompanied by a greater genetic instability that induces, in the majority of receivers, an increase of CAGn repeats. As a result, a patient who receives the disease from his father can develop a more severe form with relatively early onset (3–6 years before). The sex of the recipient does not seem to influence the process of expansion of the CAGn. It must be stressed that there is no relationship between age of parents at the time of conception and the clinical and genetic characteristics that will develop in the affected child [6].
- *CAGn vs phenotype:* the phenotype appears to be a factor independent from the genetic profile, in the sense that CAGn does not seem to determine which symptoms (motor or cognitive) the patient presents at the clinical debut
- *Progression vs age of onset* and CAGn: a later onset of disease is associated with a longer life and a better clinical outcome, indicating the early onset as a negative prognostic factor. The relationship between CAGn and clinical progression remains unclear, although a recent trial has shown that by correcting for age of onset, the correlation between CAGn repeats and disease progression significantly increases.

30.6.2 Prognostic Value of Neuroimaging

CT or MRI studies showed a progressive striatal atrophy and cortical thinning in primary motor and visual cortices and precuneus, which can precede the appearance of motor symptoms. Caudate and putamen volumes are reduced in individuals with the HD-CAG repeat expansion 9–20 years prior to onset of diagnosable HD, and could predict onset of symptoms within 2 years with 100 % accuracy. More recently, studies of functional imaging (PET and SPECT) have demonstrated a selective striatal hypometabolism (from 37 to 91 %), which can increase by 7 % per year, even preceding by several years, the emergence

of hypotrophy as seen with conventional MRI. In "clinical HD," striatal atrophy correlates with disease severity and could be an important prognostic factor at the time of diagnosis [7].

30.6.3 Clinical Issues Useful for Prognosis

Baseline performance on tasks that assess psychomotor speed, attention, visual-spatial working memory and executive function showed a predictive value that may be more accurate than the analysis of the effects of CAG repeat length and age interaction [8].

The chorea orientation index, a quantitative test of choreic symptoms, and baseline apathy scores were additional predictors of early HD progression. The Unified Huntington's Disease Rating Scale (UHDRS) is a useful clinical tool to follow disease progression in motor, cognitive, behavioral, and functional disability; however, negative motor features, such as grip force impairment, seem to be more sensitive in detecting motor deficits associated with disease progression than global clinical scores.

30.6.4 Overall Prognostic View

In pre-HD subjects, the genetic profile is the determining factor as well as some aspects of neuroimaging which are significant in population studies but not for individual cases.

Symptomatic HD usually runs its full terminal course in 10–30 years. It has been observed that the earlier in life the symptoms of HD appear, the faster the disease progresses. Juvenile onset usually results in death within 10 years.

At the time of diagnosis, some genetic factors have a prognostic weight: homozygote subjects with high CAGn and paternal transmission can expect a more rapid progression.

As long as the motor disturbances are limited to chorea and the cognitive and psychiatric impairment are not severe, resulting disability is mild with little impact on quality of life. With the progression of the disease, the deterioration of motor performances imposes a limitation on working activity, and the appearance of significant cognitive and behavioral disorders makes social and familial relationships difficult. In this stage, usually 3–8 years from onset, the patient must give up driving and the use of special tools and requires assistance in an increasing number of daily activities. Within a few months or years, with the further worsening of cognitive problems together with the need for sedative drug, there is a complete loss of role within the family and profession.

Depression may increase the risk of suicide, particularly when a person receives diagnosis supported by genetic testing and then subsequently in the middle stages of the disease when patients realize their loss of independence. In the late stage, a person with HD requires help with all activities of daily living and care, and finally is confined to a bed and unable to speak. However, he is generally able to understand language and has an awareness of family and friends. The bedridden patient in the final stages often dies from complications such as heart failure, pneumonia or other infections, injuries related to falls, or complication related to dysphagia.

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31 Extrapyramidal Diseases: Hyperkinetic Movement Disorders – Tics and Tourette Syndrome

Marco Prastaro and Floriano Girotti

Key Facts

- **Terminology and definitions** – *Tics* are semi-voluntary, sudden, rapid, brief, and non-rhythmic motor movements or phonic productions. *Tourette syndrome* (TS) is a neuropsychiatric disorder characterized by motor and phonic tics.
- **Clinical features** – *Tics* may be simple, complex, transient or chronic. *TS*: motor and vocal tics; neuropsychiatric symptoms.
- **Diagnosis** – Clinical.
  - **Genetics** – *TS*: significant multigene correlation.
  - **Imaging** – MRI (supporting role).
- **Top differential diagnoses** – *TS*: tics; Obsessive-Compulsive Disease; Psychosis.
- **Prognosis**
  - **Principles of treatment** – *TICS and TS*: antipsychotic drugs.
  - **Disability** – Intraindividual and interindividual variability *quoad valetudinem*.

Abbreviations

ADHD, attention deficit hyperactivity disorder; OCD, obsessive–compulsive disease; TS, Tourette syndrome

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31.1 Tic Disorders

31.1.1 Definition

Tics are semi-voluntary, sudden, rapid, brief, and non-rhythmic motor movements or phonic productions.

31.1.2 Clinical Features

Tics cause aimless and stereotyped motor actions (motor tics) and/or sounds (vocal tics) that are not suitable to the context. The patient declares he feels obliged to do it in order to release tension. It is possible to overpower such movements for a limited time by an endeavor of will, but the tics come back as soon as the subject's attention is distracted.

Tics are classified as "simple" or "complex". Simple tics implicate a restricted number of muscle groups. Complex tics, instead, involve several muscle groups.

31.1.3 Demographics

"Transient tic" is the most usual tic disorder and may affect up to 20 % of children during the early school years, while "chronic tic" interests up to 5 % of children [1]. Tics are defined "chronic" if present for 1 year or more.

The DSM V classifies Tourette's and tic disorders as motor syndromes registered in the section of the neurodevelopmental illnesses. This category encompasses:

- Other specified tic disorder (specify reason).
- Unspecified tic disorder.
- Provisional tic disorder.
- Persistent (chronic) motor or vocal tic disorder (specify motor or vocal).
- Tourette's syndrome, which is the combination of motor and vocal tics lasting longer than 1 year, often in comorbidity with neuropsychiatric conditions.

Treatment of tic disorders, although not habitually necessary, is analogous to treatment of TS.

31.2 Tourette Syndrome (TS)

31.2.1 Definitions

Tourette's syndrome (multiple tic syndrome) is a neuropsychiatric disorder where major clinical features are motor and phonic tics with neuropsychiatric comorbidity, which wax and wane in graveness.

31.2.2 Demographics

TS concerns people from all ethnic groups; males are affected about three to five times more than females. TS affects between 0.1 and 4 of every 1,000 girls and between 1 and 8 of every 1,000 boys [2].

The early symptoms of TS commonly occur in childhood, with the typical onset between the ages of 3 and 9 years. The assortment of vocal and motor tics differentiates the TS from the other tic disorders.

As the condition advances, clinical asset presents new neuropsychiatric symptoms. These patients are at augmented risk for the development of several comorbidities, such as attention deficit hyperactivity disorder (ADHD), obsessive–compulsive disease (OCD), anxiety, and depression [3].

31.2.3 Diagnosis

TS diagnosis requires [4]:

- Having two or more motor tics and at least one vocal tic, even though they might not continuously occur at the same time.
- Having had tics for at least 1 year. The tics can happen many times a day (classically in bouts) approximately every day, or off and on.
- Having clinical symptoms not due to taking medicine or other drugs or due to having another disease.
- Having tics that initiate before the subject is 18 years old.

31.2.4 Pathology

TS is due to hyperdopaminergic abnormalities in the basal ganglia, especially in the caudate nucleus. Etiology of TS is unknown.

31.2.5 Diagnostic Markers

MRI Has only an ancillary role in the diagnosis of TS. Its use is justified especially in the differential diagnosis of other similar neuropsychiatric diseases.

Genetics Support for the primary genetic nature of TS originates from twin research, which has shown higher concordance rates in monozygotic twin pairs than in dizygotic pairs. Multiple genetic loci [5] are surely involved in the pathogenesis of TS.

31.2.6 Top Differential Diagnoses

Psychosis; Tic Disorders; ADHD; OCD

31.2.7 Therapy

No drugs can eliminate all TS accompanying symptoms. In addition, all medications have side effects. Neuroleptics are the most common drugs used to treat TS.

31.2.8 Prognosis

TS time course is erratic but generally not poor.

The first symptoms usually occur in the head and neck area and may progress to muscles of the extremities and trunk. Motor tics commonly anticipate the development of vocal tics and simple tics frequently come before complex tics. Abnormal movements usually reach a peak in adolescence and tend to lessen in middle age.

Predictors of amplified tic harshness in adulthood encompass higher childhood tic severity, lesser fine motor control, and minor caudate dimension [6]. Additionally, the occurrence of other psychiatric comorbidities can unfavorably affect the long-term outcome of individuals with TS.

Although TS is typically lifelong and chronic, it is not a degenerative disorder and it does not prejudice intelligence. Therefore, subjects with TS have a normal life expectancy [7].

31.3 Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS)

A recent childhood disease linked to tic conditions is pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS). It is a well-defined syndrome where tics (vocal and/or motor) and/or obsessive compulsive disorders (OCD) erupt in temporal correlation to a group A beta-hemolytic streptococcal infection. Like tic disorders and adult OCD, PANDAS is due to a basal ganglia impairment. PANDAS prognosis is variable and in any case *quoad valetudinem* [8].

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Extrapyramidal Diseases: Essential Tremor

32

Marco Prastaro

Key Facts

- **Terminology and definitions** – Tremor is a rhythmic and oscillatory movement of a body portion with relatively steady frequency and mutable amplitude. Tremor can appear at "rest," during postural maintenance and/or action performance
- **Clinical features** – ET is a particular type of action tremor.
- **Diagnosis**
  - **Genetics** – ET has often autosomal dominant inheritance; sporadic ET may occur.
  - **Imaging** – Nonsignificant.
  - **Neurophysiology** – Electromyography shows alternating or unevenly synchronous contractions of reciprocally innervated agonistic and antagonistic muscles.
- **Top Differential Diagnoses** – Parkinson disease; psychogenic tremor; toxic tremor; dystonic tremor; cerebellar disease.
- **Prognosis**
  - **Principles of treatment** – *Medical*: beta-blockers and antiepileptics are the first choice; *Surgery*: DBS
  - **Disability** – Often mild; occasionally, it affects significantly quality of daily living

Abbreviations

DBS, deep brain stimulation; ET, essential tremor; VIM, ventral intermediate nucleus

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32.1 Definition

Tremor is a rhythmic and oscillatory movement of a body part with rather steady frequency and flexible amplitude. Tremor is the most usual of all movement disorders. It is due to alternating or unevenly synchronous contractions of reciprocally innervated agonistic and antagonistic muscles. In relation to movement, tremors can be categorized as "rest," "postural," or "action." Essential tremor (ET) (alias hereditary tremor; hereditary tremor; familial tremor; benign idiopathic tremor) is the most common type of action tremor, affecting up to 5–6 % of people over the age of 60 [1].

32.2 Clinical Features

ET is a chronic and gradually progressive disease. It is the most common extrapyramidal disorder, with an estimated overall prevalence of around 0.4–6 %, with no ethnic partiality. Prevalence is highest after the sixth decade.

The symptoms may initiate at any age; however, there are two most frequent onset peaks: the first, around the II decade and the second, around the VI decade. ET ordinarily begins in the arms, though it may appear in every body part. Generally, ET is bilateral and symmetrical. It happens especially during posture maintenance and goal-directed movements [2]. It is rare but ET can also occur at rest. Emotions, fatigue, and exercise habitually exacerbate ET.

32.3 Pathology

ET might be due to an aberration within the Guillain-Mollaret triangle (olivary nucleus, rubral nucleus, and cerebellum). Particularly, cerebellum seems to play a meaningful role in the pathogenesis of ET [3].

32.4 Diagnostic Markers

Consensus Statement of the Movement Disorder Society on Tremor delineated diagnostic criteria for ET [4].

- *Genetics* – Unlike other tremors, ET has a strong association with a hereditary-family component, whence its denomination: "familial tremor." Inheritance seems to follow an autosomal dominant pattern in most family cases. Sporadic cases have been also reported.

  To date, two chromosomal loci relate with ET: chromosomes 3q13 (ETM 1) [5] and 2p22-25 (ETM 2) [6].
- *Imaging* – Nonspecific. DaT-Scan, normal in ET, can be useful for differentiating essential tremor from Parkinson's disease or parkinsonisms.

32.5 Top Differential Diagnoses

Parkinson disease; psychogenic, toxic, dystonic, cerebellar tremor [7].

32.6 Principles of Treatment

Drugs used most frequently and efficaciously to treat ET are primidone and propranolol [8].

In selected cases, DBS of the ventral intermediate nucleus (VIM) of the thalamus is a viable treatment option [9]. Numerous case series, in fact, have confirmed that approximately 80 % of patients suffering from significant ET and treated with DBS have benefited from important global tremor relief [10]. VIM DBS can also amend axial tremors, with an average of 85 % decrease in head tremor and 83 % lessening in voice tremor [11].

32.7 Prognosis

Prognosis is *quoad valetudinem*.

Factors predicting probable progression comprise asymmetric tremor and unilateral onset of the initial tremor [12].

Disability ET does not implicate sensory, cognition, and life expectancy. ET disability is often mild; nevertheless, ET symptomatology can sometimes be so relevant as to prejudice many

routine activities of daily living. ET is commonly progressive in most cases.

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Extrapyramidal Diseases: Dystonia

33

Rocco Quatrale

Key Facts

- **Terminology and definitions** – Dystonia is a clinical syndrome in which sustained involuntary muscle contractions result in twisting and repetitive movements, or abnormal postures.
- **Clinical features** – Dystonia may be: (a) inherited; (b) acquired; (c) idiopathic. Dystonia can also be classified according to etiology, age at onset, body distribution.
  - Prevalence of primary (idiopathic) early-onset dystonia is 24–50 cases per million; prevalence of late-onset variants is 101–430 cases per million. Constant or intermittent, involuntary, peculiar movements may be generalized, focal, multifocal, or may be lateralized to one side of the body.
- **Diagnostic markers**
  - **Blood** non-specific in primary and idiopathic form.
  - **CSF** non-specific in primary and idiopathic form.
  - **Genetics** – A specific molecular genetic mutation has been identified for 12 forms; DYT1 is the mutated gene of the early-onset primary dystonia (before age 24 years).
  - **Imaging** – TC and MRI non-specific in primary form.

    Neurophysiology: not routinely recommended
- **Therapy** – *Medical* – Botulinum toxin, anticholinergics, baclofen, benzodiazepines, and others (levodopa, carbamazepine, and dopamine-depleting drugs).
  - **Surgical** – GPi-DBS for primary generalized, cervical dystonia, and other variants. DBS may be useful also in several secondary dystonias.
- **Prognosis** – Primary forms are usually slowly progressive. In most individuals with onset in one leg, dystonia progresses over several years. Prognosis of secondary dystonia depends on the underlying disease.

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Abbreviations

BoNT, Botulinum NeuroToxin; CP, Cerebral palsy; DBS, Deep brain stimulation; DRD, Dopa-Responsive Dystonia; GMFCS, Gross Motor Function Classification System; GPi, Globus Pallidus internus; MRI, Magnetic Resonance Imaging; TMS, Transcranial Magnetic Stimulation

33.1 Prognosis of Dystonia

33.1.1 Definition

Dystonia is a movement disorder characterized by uncontrollable sustained or intermittent muscle contractions causing abnormal, often repetitive, movements and/or postures [1].

33.1.2 Demographics

The prevalence of early-onset dystonia ranges from 24 to 50 cases per million, with a peak age of onset in the first and second decade of life; the prevalence of late-onset dystonia ranges from 101 to 430 cases per million. Hand dystonia occurs at 30–40 years with male predominance; cranio-cervical dystonia appears in subjects over the age of 40 and is more frequent in women [2].

33.1.3 Clinical Features and Classification

Dystonia can be classified clinically according to age of onset, body distribution, temporal pattern, associated features, and etiology (inherited, acquired, or idiopathic) [1]. Dystonic movements are typically sustained, repetitive, twirling, and may be similar to tremor, which may start or worsen with voluntary activity. Non-motor components of dystonia may be important and include abnormalities in sensory and perceptual functions, as well as in neuropsychiatric, cognitive, and sleep domains [3].

Five features specify clinical characteristics: age at onset, body distribution, temporal pattern of dystonic movements, coexistence of other movement disorders, and additional neurological manifestations [1].

Dystonia that begins in childhood is more likely to have a recognizable cause, and is more likely progressive from focal to generalized. The body distribution of dystonic movements may change over time, typically with progression to previously uninvolved sites [4].

33.2 Genetics

Dystonia is a multifactorial disorder, in which one or more genes combine with environmental factors to reach the threshold of disease.

Regardless of possible underlying genetic abnormality, the pattern of transmission in primary dystonia is autosomal dominant in early- and late-onset dystonia with penetrance rates of 40–60 % and 20 %, respectively [5].

Inherited group The genetic cause has been identified in 25 forms of dystonia. Autosomal dominant dystonias include the DYT1 form (the most common) and others. The autosomal recessive group includes numerous metabolic disorders.

Acquired group may be "idiopathic" or due to a known specific cause (perinatal brain injury, infection, psychogenic, etc.)

33.3 Diagnostic Markers

Clinical feature and serial single-gene or multigene molecular genetic testing are the main diagnostic tools.

Imaging Neuroimaging studies are usually normal in idiopathic dystonia and not routinely required. MRI is the investigation of choice in detecting secondary dystonic syndromes.

Neurophysiology All neurophysiological reports are observational studies without controls (Class IV, level of evidence).

EMG recordings from various muscles may contribute to the clinical assessment and planning the target of botulinum toxin.

Somatosensory evoked potentials can detect giant cortical potentials. Sensory perception and somatosensory temporal discrimination threshold abnormalities are a generalized feature of dystonias, and they are a tool for screening subclinical sensory abnormalities [6].

33.4 Therapy

Medical Anticholinergics, particularly trihexyphenidyl, at a mean dosage of 30 mg/die, are the established first-line oral medications for generalized and segmental dystonia, and can be useful for symptomatic treatment of secondary dystonia. Baclofen, benzodiazepines, and levodopa may be employed.

Tetrabenazine, a presynaptic depleter of dopamine and a weak dopamine-receptor–blocking agent, produced marked improvement in two-thirds of patients with focal and generalized, but was associated with frequent side effects [7]. Levodopa may provide benefit in the dopa-responsive dystonia (DRD), in some patients with DYT1 dystonia and, inconstantly, in secondary forms.

Intrathecal baclofen infusion gave conflicting results in generalized and in secondary dystonias associated to spasticity or pain (cfr. in dystonia from cerebral palsy (CP) [8].

Botulinum Toxin (BoNT) is the first-line treatment for focal and task-specific dystonias.

Surgery Deep brain stimulation (DBS) of globus pallidus internus (GPi) allows significant reduction in dystonic symptoms and functional disability, and it has become a crucial treatment for patients with refractory primary generalized dystonia. The efficacy of pallidal DBS for secondary dystonia varies from no benefit to dramatic improvement. Bilateral GPi-DBS seems effective in "status dystonicus."

33.4.1 Prognosis

Literature assessing the prognosis of dystonic syndromes is scarce and incomplete. Age at onset and severity of dystonia, its duration, proportion of life lived with the symptoms, nature and timing of intervention are all factors likely to influence the outcome.

Dystonic syndromes can be static, progressive, or intermittent [1]; their behavior in time has further prognostic significance.

Clinical worsening of progressive dystonic syndromes is poorly influenced by compensatory phenomena or alleviating maneuvers, with consequent negative neurological and psychological impact.

The persistent forms of dystonia generally display a more severe course, with early motor impairment, osteo-articular deformity and easier development of comorbidities.

In child dystonia, there was significant difference in duration of dystonia and in proportion of life lived with dystonia (dystonia duration normalized to age) between the primary/primary-plus, secondary dystonia/Cerebral Palsy (CP), heredodegenerative and secondary-static dystonias. The greater severity of functional impairment in patients with secondary compared to primary/primary-plus dystonia probably relates to coincident spasticity or other conditions that impair motor function and worsens the prognosis. Among young people, only 32.6 % of patients with dystonia of different etiology have had a period of normal motor development.

Finally, the best clinical evolution with consequent better prognosis of idiopathic dystonias is confirmed by the distribution of Gross Motor Function Classification System (GMFCS) levels across the different classes, with higher clinical functioning (GMFCS levels I–III) seen in the Primary/Primary-plus forms (37/49 or 75 %) compared with secondary dystonia groups (29/230 or 13 %) [9].

The idiopathic forms are usually slowly progressive. In most individuals with onset in one leg, dystonia progresses over several years. A classic example is early-onset DYT1 dystonia that typically presents in childhood or adolescence and usually starts in a limb, gradually, or, in many patients, quickly progressing to a generalized form with consequent worsening of quality of life and prognosis [10]. Many exceptions to this typical presentation have been reported, especially in carriers of DYT1 mutation with focal or segmental dystonia of adult onset in which the clinical evolution and prognosis are less severe [11]. Four dystonia-plus syndromes with specific genetic characterizations are included in the inherited group of dystonia. All these forms have variable temporal evolution; only the dopa-responsive dystonia (DRD, DYT5) has a good prognosis, related to prolonged response to dopaminergic therapy [12].

Prognosis of secondary dystonia mainly depends on the underlying disease. The presence of other neurological or systemic features can worsen the development of clinical picture.

The underlying mechanisms of psychogenic dystonia are unclear, but a high prevalence of neuropsychiatric illness has previously been reported. The outcome of this syndrome is poor; less than 25 % of patients improve, major subsidence of symptoms is obtained in only 6 %; continued worsening takes place in a third [13].

Therapeutic options can strongly modify the prognosis of dystonia.

BoNT treatment continues to be the first choice for most types of focal dystonia; it improves quality of life in all focal dystonias, particularly blepharospasms and cervical dystonia [14]. Long-term studies on the efficacy and safety of BoNT/A recommended that BoNT injections should also be performed in focal upper extremity dystonia, and adductor laryngeal dystonia (probably effective). A low level of evidence was found for focal lower limb dystonia (possibly effective). In patients with different dystonias followed for >12 years, there was no decline of efficacy. In conclusion, repeated treatments with BoNT are safe and efficacious over many years [15].

DBS Long-term electrical stimulation of the globus pallidus internus (GPi) is an established effective treatment for various types of dystonias. GPi-DBS obtains a clear reduction in dystonic disorders and relative disability, with long-lasting clinical improvement [16].

DBS is efficacious in primary generalized or segmental forms of dystonia, in Complex cervical dystonia, and tardive dystonia, if conservative approaches fail.

GPi-DBS provided marked benefit, with improvement of dystonia motor scores ranging between 34 and 88 % and disability scores ranging between 40 and 50 %, even if longer duration of dystonia correlated negatively with surgical outcome [17].

Quality of life improves with GPi DBS, both in patients with Primary segmental and generalized symptoms. Best results with pallidal DBS were reported in primary generalized dystonia. DYT1 dystonia improved from 40–90 % [18], and even adult patients with non-DYT1 primary generalized dystonia can achieve equivalent benefit [19]. The mean motor improvement is around 54 % in primary generalized dystonia, and the mean improvement of disability reaches 44 % at 1-year follow-up. Long-term efficacy was still evident after more than 5 years of follow-up [20]. Neurostimulation significantly decreased depression, and quality of life had a statistically significant improvement of 29.8 % against 11.4 % in the placebo group [21].

The impact of GPi on secondary dystonia, in general, is much less pronounced. Patients with dystonia and choreoathetosis due to cerebral palsy may achieve limited benefit; motor scores improve from 10 to 40 gaining acceptable satisfaction in some patients [22].

Gpi-DBS obtains benefits in tardive dystonia similar to those of Primary dystonia [23].

In conclusion, although no predictive factors have been definitively established, several possible prognostic factors for DBS efficacy in dystonia include lower preoperative severity score, younger age at surgery, presence of DYT1

mutation, shorter duration of disease, and lack of fixed skeletal deformity [24].

Furthermore, prognosis of dystonia depends largely on the age of onset, the clinical characteristics (focal vs generalized), the etiology (inherited vs secondary or idiopathic), and therapeutic tools. In general, dystonia is a pathology that affects quality of life, the therapeutics options are always hard to bear, and patients often necessitate constant support from caregivers. On the other hand, dystonia usually does not affect the duration of life. In the last 20 years, DBS and botulinum toxins secured a satisfying quality of life to many dystonic people.

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Ataxias and Cerebellar Degenerations

34

Caterina Mariotti and Franco Taroni

Key Facts

- **Terminology and definitions** – Ataxias and cerebellar degenerations are Heterogeneous group of disorders characterized by impaired coordination in the voluntary movements.
- **Clinical features** – Most distinctive features are progressive gait and limbs incoordination, disequilibrium, dysarthria, and eye movement disturbances.
- **Diagnostic markers** – In Acquired forms: evidence of toxic agents or concomitant illness; in hereditary ataxias evidence of familiarity or compatible clinical history and phenotype.
  - **Blood** – Abnormal: liver enzymes, electrolytes, heavy metals, TSH, vitamin E, B1, B6, B12. Glutamic acid, GAD, onconeural Ab (acquired forms).
  - **Genetics** – Next Generation Sequencing for hereditary ataxias.
  - **MRI** – Spinal cord posterior/lateral column lesions (B12 deficiency) in acquired ataxias. Pure cerebellar atrophy (SCA, toxic, deficiency, autoimmune). Ponto-cerebellar atrophy (SCA 1–2, olivopontocerebellar atrophy, MSA-C). Cervical cord atrophy (FA, AVED).
- **Therapy** – Vitamin B1 supplementation (alcoholic syndromes, malabsorption), vit. 12 (combined sclerosis), vit. E in recessive ataxia with vitamin E deficiency, Coenzyme Q10 supplementation in recessive ataxias with CoQ10 deficiency.
  - **Prognosis** – good if promptly treated for acquired infectious or toxic ataxia. Chronic progressive degenerative disease course for inherited forms.

Abbreviations

AD, autosomal dominant; ADCA, autosomal dominant cerebellar ataxias; AR, autosomal recessive; ARCA, autosomal recessive cerebellar ataxias; AT, ataxia-telangiectasia; AVED, ataxia with vitamin E deficiency; CTX, cerebrotendinous xanthomatosis; DRPLA, dentato-rubro-pallidal-luysian atrophy; EA, episodic ataxias; FA/FRDA, Friedreich's ataxia; FXTAS, Fragile X tremor/ataxia syndrome; ILOCA, Idiopathic late onset cerebellar ataxia; MSA, multiple system atrophy; MSA-C, MSA with predominant cerebellar ataxia; MSA-P, MSA with predominant parkinsonism; N.s., non-specific; PDC, paraneoplastic cerebellar degeneration; RD, Refsum disease; SCA, SpinoCerebellar Ataxias; SAOA, sporadic adult-onset ataxia of unknown etiology

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34.1 Definitions

The term ataxia means "lack of order", i.e., absence of coordination in the voluntary movements. Ataxia may be due to pathological changes in the cerebellum or in central and sensory pathways, but it is more frequently referred to the diseases involving cerebellar structures and spinocerebellar tract degeneration.

34.2 Epidemiology

Cerebellar ataxias represent a heterogeneous group of rare disorders with an estimated prevalence of 15–20: 100,000 [1].

34.3 Clinical Features and Clinical Classification

The most distinctive clinical features are progressive gait and limbs incoordination, disequilibrium, dysarthria, and eye movement disturbances. A number of the cerebellar and spinocerebellar diseases are complicated by the presence of additional neurological deficits, including pyramidal or extrapyramidal signs, peripheral neuropathy, optic atrophy, retinopathy, and cognitive decline. A few forms are also characterized by non-neurological manifestations such as cardiomyopathy, immunologic and skeletal abnormalities. Age at onset, severity of symptoms, disease progression, and prognosis are largely variable, depending on the underlying pathology.

Classifications may take into consideration the age at onset, the acute or chronic presentations of symptoms, and the familial manifestation of the phenotype.

The cause-based classification of degenerative spinocerebellar ataxias distinguishes three principal subgroups:

1. Acquired forms due to toxic agents or concomitant illness.
2. Hereditary ataxias, including the vast groups of the autosomal dominant and recessive spinocerebellar ataxias, and the rare cases presenting a mitochondrial (maternal) inheritance or an X-linked pattern of transmission.
3. Late-onset sporadic ataxias of unknown cause. The most frequent form of this group is represented by the clinical phenotypes of multiple system atrophy (MSA).

34.4 Acquired Cerebellar Ataxias

34.4.1 Terminology and Definitions

The acquired ataxias are usually progressive forms due to exogenous causes, including toxic agents (mercury, lead), alcohol, drugs, infectious or inflammatory diseases, endocrinologic abnormalities (hypothyroidism), acquired vitamin deficiency, and immunological and paraneoplastic syndromes. Usually the presentation is acute or subacute [1–4].

34.4.2 Clinical Features

Clinical features include disequilibrium, limb incoordination, oculomotor abnormalities, and dysarthria. Focal structural lesions of the cerebellum, such as malformations, abscess, hemorrhage, focal demyelination, or neoplastic lesions may cause an acute onset of vomiting and headache and unilateral neurological deficits. Focal cerebellar lesions are promptly identified at brain MRI imaging examination (Table 34.1).

Diffuse cerebellar involvement is more often associated with toxic, metabolic, and paraneoplastic syndromes, and the presentation of symptoms may be subacute or chronic. In these latter forms, cerebellar atrophy is a non-specific feature and it may involve predominantly the vermis (as in chronic alcoholic degeneration), or the cerebellar hemispheres and the adjacent pontine and spinal cord structures.

In alcoholic cerebellar degeneration, the clinical syndrome is characterized by prominent ataxia of gait and legs, with difficulties in standing and frequent sway. In addition to the toxicity of alcohol, the clinical presentation may be

Table 34.1 Diagnosis, laboratory, and neuroimaging tests in acquired ataxias

Diagnosis	Blood test	CSF	Brain MRI	Therapy
Mass lesions			Glioma, menigioma, abscess, focal malformations, cerebellar lesions, tumor	
Toxic agents, alcohol, drugs	Hb, Ht, liver tests, antiepileptic drugs, litium, statins, electrolytes, heavy metals		Cerebellar atrophy	
Endocrine disorders	thyroid hormone (TSH), Anti-TPO antibodies			
Malabsorption	Vitamin E, B1, B6, B12		Cerebellar, pontine, spinal cord posterior/ lateral columns lesions	
Auto-immune disorders	antibodies to glutamic acid decarboxylase (GAD)		Cerebellar atrophy	
Celiac disease (gluten ataxia)	Antigliadin, tissue transglutaminase, endomysium antibodies		Cerebellar atrophy	
Demyelinating disorders		Protein, electrophoresis IgG index,	Demyelinating lesions	
Infections	Systemic evidence of infectious, viral screening infectious	Lymphocytes, glucose, viral infectious screening		
Paraneoplastic syndromes	Onconeuronal antibodies	Onconeuronal antibodies	MRI non-specific; Cerebellar atrophy	
FA, AVED			Cervical cord atrophy	
SCA			Cerebellar or ponto-cerebellar atrophy	

aggravated by the onset of other concomitant symptoms due to vitamin B1 deficiency (Wernicke's encephalopathy). Vitamin deficiencies may result from malabsorption and bowel diseases, causing a spinocerebellar degeneration associated with axonal sensory neuropathy as in the case of vitamin E deficiency, or combined spinal cord degeneration in B12 defect.

Severe and subacute truncal ataxia, limbs incoordination, and dysarthria may represent the clinical presentation in paraneoplastic cerebellar degeneration with neurological deficits most often preceding the detection of the underlying tumor [1, 5] (see Chap. 27).

34.4.3 Diagnostic Markers

MRI brain scan can exclude structural lesions or recognizable disease-specific abnormalities.

Vitamin deficiencies, endocrinological disorders, coeliac disease, immunological and paraneoplastic syndromes may be screened by appropriate hematochemical tests [6, 7] (Table 34.1). Chronic cerebellar damage may also be associated with drug compounds, such as lithium, phenytoin, amiodarone, toluene, and the anti-cancer drugs 5-fluorouracil and cytosinearabinoside. Heavy metals (lead compounds, mercury, and thallium) are cerebellar toxic agents.

34.4.4 Principles of Treatment

Of the most important therapeutic measures in ataxias caused by toxic agents is the immediate cessation of exposure. Strict abstinence and vitamin B1 supplementation improves alcoholic ataxia.

A multivitamin preparation, including vitamin E supplementation, is recommended in malabsorption syndromes.

In paraneoplastic cerebellar degeneration (PCD) (see Chap. 27), the obvious approach is the treatment of the underlying tumor; however, only exceptional cases respond to tumor removal or immunosuppressive therapy (plasma exchange, intravenous immunoglobulins, or steroids), with the exception of PCD associated with anti-Tr and anti-mGluR1 antibodies in Hodgkin's disease.

There is no established treatment for anti-GAD ataxia, although improvement of ataxia after steroids and intravenous application of immunoglobulins has been reported [1, 3, 4]. The treatments of infectious and demyelinating diseases of the nervous system are described in more details in dedicated chapters (see Chaps. 7, 8 and 11).

34.4.5 Prognosis

Prognosis of the acquired infectious or toxic cerebellar ataxia may be good when the specific etiology agents can be promptly recognized and treated. These forms are potentially reversible with the treatment if this is given within the first months after manifestation of ataxia. Residual cerebellar deficits may become permanent when associated to cellular loss and damage to the cerebellar structures. The cerebellar degeneration associated with immune factors has a chronic progressive disease course, and may cause moderate to severe motor and cognitive disability.

34.5 Hereditary Degenerative Ataxias

34.5.1 Terminology and Definitions

The inherited cerebellar/spinocerebellar syndromes are subdivided by the mode of inheritance into autosomal dominant (AD), autosomal recessive (AR), X-linked and mitochondrial disorders [8, 9].

A familial disorder affecting successive generations is suggestive of autosomal dominant cerebellar ataxias (ADCA). Genetic classification of autosomal dominant cerebellar ataxias (ADCAs) includes more than 35 subtypes of SpinoCerebellar Ataxias (SCA), which are numbered in the order of locus or gene description (SCA1-SCA36) with approximately 20 genes identified. In addition, the ADCA group also includes the episodic ataxias (EA), with 7 loci (EA1-7) and 4 genes identified, and the dentato-rubro-pallidal-luysian atrophy (DRPLA) [10–13].

An X-linked mode of inheritance is associated with the Fragile X tremor/ataxia syndrome (FXTAS).

The autosomal recessive cerebellar ataxias (ARCA) are rare, genetic heterogeneous diseases with more than 20 different clinical and genetic subtypes [8, 9, 14]. ARCA usually begin before the age of 20 years. Friedreich's ataxia (FRDA) and ataxia-telangiectasia (AT) are the most frequent forms. The presence of multiple affected sibs in a single generation or consanguinity in the parents supports the idea of an autosomal recessive mode of inheritance. In ARCAs, as in other autosomal recessive diseases, carriers of only one disease causing mutation in a gene (heterozygote) are not at risk of developing the disease.

34.5.2 Clinical Features

*SCA*s are diseases of the entire nervous system, and present a wide and overlapping range of neurological symptoms including ataxia of gait and limbs, dysarthria, spasticity, extrapyramidal movement disorders, retinopathy, optic atrophy, peripheral neuropathy, sphincter disturbances, and cognitive impairment [10–13]. All patients also present oculomotor disturbances, of cerebellar and supranuclear origin. Later in the disease, pontine involvement may cause slow saccades and ophthalmoparesis [10–13].

Men with a *fragile X* premutation present in the sixth decade with progressive intention tremor, ataxia, and parkinsonism, cognitive decline, and peripheral neuropathy.

In EAs, the disease presents with recurrent, discrete episodes of ataxia, giddiness, and vertigo with or without interictal abnormalities.

There are over 35 SCAs genetic subtypes, and their prevalence varies between different populations. The most frequent subtypes are those caused by expanded CAG repeats (SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, and DRPLA), and among these, SCA3 is the commonest subtype worldwide. The clearest genotype-phenotype correlation is found between the CAG repeat length and the age at onset, disease severity, and progression.

Age at onset is usually in adulthood for the ADCA, and more frequently before age 20 in ARCA and in EA. The course of all these diseases is chronic progressive.

Friedreich's ataxia is the most common of the autosomal recessive ataxias and the most common hereditary ataxia overall with a prevalence of approximately one person in 50,000 in Caucasian populations [14, 15]. Age at onset is typically 5–25 years. Clinically, Friedreich's ataxia is characterized by early-onset progressive gait and limb ataxia, dysarthria, loss of vibration and proprioceptive sense, areflexia, abnormal eye movements, and pyramidal weakness. Cardiomyopathy, diabetes, scoliosis, and pes cavus are other common systemic complications [14, 15].

34.5.3 Diagnosis of Inherited Cerebellar Ataxias

34.5.3.1 Genetic Tests

In case of a family history compatible with autosomal dominant inheritance, the initial genetic testing should include SCA1, 2, 3, 6, 7, and 17, as they comprise the most common forms of SCAs. This screening may allow a genetic diagnosis in 50–60 % of ADCA cases. Diagnosis of the other SCAs genetic subtypes requires wide genetic screening and the search of specific mutations [8, 16, 17] (Table 34.2).

Table 34.2 Autosomal dominant ataxias: genetic subtypes and main clinical features

Disease	Gene	Main associated symptoms	Age at onset
SCA1	ATXN1	Dementia, nystagmus, slow saccades pyramidal signs, neuropathy	4–74
SCA2	ATXN2	Dementia, slow saccades, hyporreflexia, amyotrophy, neuropathy, myoclonus, rare Parkinsonism	6–67
SCA3	ATXN3	Nystagmus, diplopia, ophthalmoplegia, eye-lid retraction, Parkinsonism, spasticity neuropathy	5–65
SCA4	Puratrophin-1 (PLEKHG4)	Pure cerebellar syndrome or associated with axonal sensitive neuropathy	19–72
SCA5	β-III Spectrin (SPTBN2)	Pure cerebellar syndrome, down-beat nystagmus, bulbar symptoms in juvenile cases. Slow progression	15–50
SCA6	CACNA1A	Pure cerebellar syndrome, sometimes episodic ataxia at onset, double vision, pyramidal signs, deep sensory loss, migraine. (Disease is allelic to episodic EA2 and Familial Hemiplegic Migraine)	19–77
SCA7	ATXN7	Retinal degeneration, ophthalmoplegia, pyramidal signs	0.1–76
SCA8	ATXN8 (Kelch-like)	Sensory neuropathy, slow progression	0–73
SCA10	ATXN10	Seizures, pyramidal and extrapyramidal signs	10–40
SCA11	TTBK2	Pure cerebellar syndrome, hyperreflexia, very slow progression	17–33
SCA12	PPP2R2B	Dementia, tremor of head and upper extremities, Parkinsonism, hyperreflexia, neuropathy	8–55
SCA13	KCNC3	Delayed motor development, mental retardation in some, seizures	4–60
SCA14	PRKCG	Cognitive deficits, facial myokymia, rare myoclonus, and focal dystonia	10–59

(continued)

Table 34.2 (continued)

Disease	Gene	Main associated symptoms	Age at onset
SCA15/ SCA16	ITPR1	Pure cerebellar syndrome or associated with head tremor. Slow progression	10–66
SCA17	TBP	Dementia, psychosis, chorea, seizures	10–70
SCA18	Unknown	Limb weakness, axonal sensory neuropathy (EMG shows denervation)	13–27
SCA19	Unknown	Dementia	20–45
SCA20	Unknown	Dysphonia, palatal tremor, spasmodic cough, bradikynesia, dentate calcification	19–64
SCA21	Unknown	Cognitive impairment, Parkinsonism	6–30
SCA22	Unknown	Pure cerebellar syndrome	10–46
SCA23	PDYN	Pure cerebellar syndrome or associated with pyramidal signs, sensory loss	43–56
SCA25	Unknown	Sensory neuropathy	1.5–39
SCA26	Unknown	Pure cerebellar syndrome, slow progression	26–60
SCA27	FGF14	Tremor, dyskinetic movements, psychiatric signs	12–40
SCA28	FG3L2	Ophthalmoplegia, hyperreflexia, slow progression	12–36
SCA29	Unknown	Non-progressive, highly variable phenotype	0–1
SCA30	Unknown	Minor pyramidal signs	45–76
SCA31	TK2 and BEAN	Late-onset, often associated with sensorineural hearing impairment	
SCA32	Unknown	Cognitive impairment, azoospermia, testicular atrophy	
SCA35	TGM6	Upper limb ataxia, spasmodic torticollis	
SCA36	NOP56	Motor neuron involvement (hyperreflexia and lower motor neuropathy with fasciculations and skeletal muscle atrophy)	
DRPLA	ATN1	Dementia, chorea, myoclonus, seizures	10–59
EA1	KCNA 1	Muscle spasms, interictal myokymia and jerking movements, chorea at onset. Attack duration: seconds to minutes.	2–15
EA2	CACNA1A	Down-beat nystagmus, dysarthria, vertigo, muscle weakness, migraine. Interictal ataxia and nystagmus. Attack duration: hours to days.	2–20
EA3	Unknown	Myokymia, migraine, tinnitus, vertigo, dysarthria. Attack duration: 1 m-6 h.	1–42
EA4/ PATX	Unknown	Vertigo, diplopia. Interictal nystagmus and saccadic smooth pursuit. Attack duration: brief.	23–60
EA5	CACNB4β4	Vertigo. Interictal nystagmus, ataxia, epilepsy. Attack duration: hours.	3–19
EA6	SLC1A3 (EAAT1)	Cognitive impairment. Interictal epilepsy, migraine, ataxia, motor delayed milestones. Attack duration: hours/day.	<20
EA7	Unknown	Vertigo, dysarthria, muscle weakness. Attack duration: hours/days.	13–19
FXTAS X-linked	FMR1	Intention tremor, nystagmus, mild parkinsonism, neuropathy	>50

ATXN1,2,3,7,8,10 Ataxin-1,2,3,7,8,10; *CACNA1A* Calcium Channel, Voltage-Dependent, P/Q Type, Alpha-1a Subunit; *CACNB4β4* Calcium Channel, Voltage-Dependent, Beta-4 Subunit; *DRPLA* Dentatorubral-Pallidoluysian Atrophy; *EAAT1* Excitatory Amino Acid Transporter 1; FGF14: Fibroblast Growth Factor 14; *ITPR1* Inositol 1,4,5-Triphosphate Receptor, Type 1; *KCNA 1* Potassium Voltage-Gated Channel; *KCNC3* Potassium Channel, Voltage-Gated, Shaw-Related Subfamily, Member 3; *MTP* Microsomal Triglyceride Transfer Protein; *PLEKHG4* Pleckstrin Homology Domain-Containing Protein, Family G, Member 4; *PPP2R2B* Protein Phosphatase 2, Regulatory Subunit B, B; *PRKCG* Protein Kinase Cγ; SLC1A3: Solute Carrier Family 1 (Glial High Affinity Glutamate Transporter), Member 3; *SPTBN2* Spectrin, Beta, Non-erythrocytic, 2; *TBP* TATA Box-Binding Protein; *TTBK2* Tau Tubulin Kinase 2; *FXTAS* Fragile X Tremor/Ataxia Syndrome; *FMR1* Fragile X Mental Retardation Gene

The Fragile X tremor/ataxia syndrome (FXTAS) is caused by an expanded CGG trinucleotide repeat in the FMR1 gene, ranging in size from 55 to 200 repeats ('premutations'). Full repeat expansions (>200 repeats) result in fragile X mental retardation syndrome.

The diagnosis of specific subtypes is complicated by the vast overlap of the phenotypes and the variability of clinical features (Table 34.2).

If an autosomal recessive ataxia is suspected, FRDA mutations must be always excluded. Diagnosis of other recessive forms may be guided by biochemical findings such as reduced levels of vitamin E or albumin, increased levels of cholesterol or alpha-fetoprotein, reduced concentration of Coenzyme Q10 in muscle [14, 16] (Table 34.3).

The genetic work-up in inherited disorders will change over the upcoming years due to the diagnostic utility of new techniques such as "Next Generation Sequencing" or even whole exome and genome sequencing for selected cases [4].

34.5.3.2 Imaging

SCAs: *Brain MRI* imaging may show a predominant cerebellar atrophy, or a more diffuse cerebral atrophy involving the brain stem structures, the putamen and caudate nuclei, and also the cerebral cortex.

ADCA ARCA, EAs: Mild cerebellar atrophy may be found in the late stage of the diseases.

Friedreich ataxia: Atrophy of the cervical spinal cord.

FXTAS: Symmetric regions of increased T2 signal intensity in the middle cerebellar peduncles and adjacent cerebellar white matter are considered typical of fragile X this neurological condition.

34.5.4 Principles of Treatment

Despite the large number of genetic and pathogenic studies, for the vast majority of autosomal

Table 34.3 Autosomal recessive ataxias: genetic subtypes, clinical and biochemical features

Disease	Gene	Main clinical features	Age at onset	Biochemical findings
FRDA	FRDA1	Saccadic smooth pursuit, fixation instability, saccadic dysmetria, dysarthria, Babinski sign, deep sensory loss, neuropathy cardiomyopathy, diabetes	2–55	
AVED	αTTP	Head titubation, nystagmus, saccadic smooth pursuit, retinopathy	2–52	Low plasma levels of vit.E
ABL	MTP	Steatorrhea, areflexia, sensory ataxia, retinal degeneration, dissociated nystagmus on lateral gaze, slow saccades, neuropathy	0–20	Acanthocytes, reduced serum LDL and VLDL
AOA1	APTX	Oculomotor apraxia, fixation instability, saccadic pursuit, gaze-evoked nystagmus, hypometric saccades, neuropathy, choreoathetosis, mild mental retardation	1–29	Hyperchole-sterolemia, hypoalbumi-nemia
AOA2	SETX	Oculomotor apraxia (Rare), saccadic pursuit, slow saccades, fixation instability, choreoathetosis, motor neuropathy with amyotrophy	3–30	Increased AFP
AT	ATM- gene	Telangiectasia, immune deficiency, predisposition to cancer, oculomotor apraxia, increased latency of saccades	1–4	Chromosomal instability, increased AFP
ATLD	MRE11	Similar to AT, milder course	1–7	Possible chromosomal instability, normal AFP
FXTAS	FMR1	Intention tremor, nystagmus, mild parkinsonism, neuropathy	>50	

FRDA Friedreich Ataxia; *ABL* Abetalipoproteinemia; *AFP* Alpha-Fetoprotein; *AOA1* Ataxia with Oculomotor Apraxia Type 1; *AOA2* Ataxia with Oculomotor Apraxia Type 2; *APTX* Aprataxin; *AT* Ataxia-Teleangiectasia; *ATLD* Ataxia-Teleangiectasia-like Disorder; *ATM* Ataxia-Teleangiectasia Mutated (gene); *ATTP* α-Tocopherol Transfer Protein; *AVED* Ataxia with Vitamin E Deficiency; *MRE11*: Meiotic Recombination 11; S. Cerevisiae, Homolog, A; *SETX* Senataxin

dominant, X-linked, and recessive inherited ataxias, the possibility of effective therapies is still lacking. Current treatment is only symptomatic and management of ataxia relies on physiotherapy. Palliative care is needed in the later disease stage.

Only a few of the recessive ataxias are treatable.

In ataxia with vitamin E deficiency (AVED) a lifelong oral administration of high-dose vitamin E (800–1200 mg a day) is recommended. If the treatment is started early in the disease, some symptoms may disappear.

In abetalipoproteinemia, early treatment with 150 mg of a-tocopherol per kilogram and vitamin A can reduce symptoms.

In recessive ataxia with coenzyme Q deficiency (see Chap. 20), the treatment with high doses of CoQ10 ameliorated the ataxia in some patients.

Two metabolic diseases, cerebrotendinous xanthomatosis (CTX) (see Chap. 19) and Refsum disease (RD) (see Chap. 35), in which ataxia may be a predominant symptom, may also benefit from specific treatment. Chenodeoxycholic acid may stabilize clinical signs in CTX, and a dietary restriction of phytanic acid and a high-calorie diet is advised in patients with RD [4, 14, 18].

34.5.5 Prognosis of Inherited Cerebellar Ataxias

Inherited cerebellar ataxias greatly differ with respect to age of onset, rate of disease progression, and survival. A recent multicentric, longitudinal, European study with a cohort of 526 patients with the most common SCA subtypes (SCA1, SCA2, SCA3, or SCA6) demonstrated that the median survival time of patients with SCA ranges from 21 to 25 years. The disease progression was found to be fastest in SCA1 followed by SCA2 and SCA3, in which progression rates did not differ. Disease progression was slowest in SCA6 [19]. These findings confirmed previous retrospective observations on the natural history of degenerative ataxias [20]. Median age of onset in these SCA types is similar, ranging from 30 to 46 years. In general, purely cerebellar types of degenerative ataxias have a slower progression than the subtypes characterized by the occurrence of various non-cerebellar symptoms. Time until confinement to wheelchair is 27 years in SCA with pure cerebellar phenotype and is 17 years in SCA with complex clinical and neurological presentation [20].

Among the groups of recessive cerebellar ataxias, the disease progression in FRDA patients was found to be faster in comparison with other forms. The median latency to confinement to wheelchair was 11 years, and approximately 75 % of the patients survive for 34 years after disease onset. Onset before the age of 20 years was associated with a shorter time before becoming wheelchair-bound [20].

34.6 Multiple System Atrophy (MSA)

See Chap. 29, Parkinsonisms and Chap. 36.

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Disorders of Peripheral Nerves

35

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Abbreviations

AAN, American Academy of Neurology; A-CIDP, acute-onset CIDP; AD, autosomal dominant; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AIP, acute intermittent porphyria; AL, amyloidosis light-chain; ALS, amyotrophic lateral sclerosis; AMAN, acute motor axonal neuropathy; APOA1, apolipoprotein A1; AMSAN, acute motor-sensory axonal neuropathy; AR, autosomal recessive; BBE, Bickerstaff's brain-stem encephalitis; BMI, body mass index; C, campylobacter; CAN, cardiovascular autonomic neuropathy; CB, conduction block; CDAS, CIDP disease activity status; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMAP, compound motor action potential; CMT, Charcot-Marie-Tooth (CMTX = X-dominant CMT, CMT1 = demyelinating subtypes, CMT2 = axonal subtypes); CMT-NS, CMT-neuropathy score; CMV, cytomegalovirus; CNS, central nervous system; CB, conduction block; cPAN, cutaneous polyarteritis nodosa; CSA, cross-sectional area; CSF, cerebrospinal fluid; CTS, carpal tunnel syndrome; CV, conduction velocity; DM, diabetes mellitus; DML, distal motor latency; dSMA, distal spinal muscular atrophy; DSP, distal symmetric polyneuropathy; EFNS, European Federation of Neurological Societies; EDX, electrodiagnosis; EMG, electromyography; ENG, electroneurography; ERT, fibrillation potentials, enzyme replacement therapy; FAP, familial amyloid polyneuropathies; FP, fibrillation potential; GBS, Guillain-Barré syndrome; GSN, gelsolin; HMSN, hereditary motor sensory neuropathies; HNA, hereditary neuralgic amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsies; HRV, heart rate variability; HSAN, hereditary sensory and autonomic neuropathies; HSCT, allogenic hematopoietic stem cell transplantation; HSP, hereditary spastic paraplegias; IVIg, intravenous immunoglobulin; LLN, lower limit of normal; LSRP, radiculoplexopathy; MAG, myelin associated glycoprotein; MFS, Miller-Fisher syndrome; MGUS, monoclonal gammopathy of undetermined significance; MNGIE,

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mitochondrial neurogastrointestinal encephalopathy; MRC, Medical Research Council; MRI, magnetic resonance imaging; MU, motor unit; NCV, nerve conduction velocities, (M = motor, S = sensory); NSAIDs, non-steroidal anti-inflammatory drugs; NSVN, non-systemic vasculitic neuropathy; PE, plasma exchange; OLT, orthotopic liver transplantation; PNI, peripheral nerve injury; PNS, peripheral nervous system; POEMS, peripheral neuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; QSART, quantitative sudomotor axon reflex testing; QST, quantitative sensory testing; SAP, *sensory* action *potentials*; SC, Schwann cell; SFN, small-fiber-neuropathy; SNAP, sensory nerve action potential; SW, sharp waves; SVN, systemic vasculitic neuropathies; T1DM and T2DM, type 1 DM and type2 DM; TTR, transthyretin; ULN, upper limit of normal; US, ultrasonography; VEGF, vascular endothelial growth factor; WM, Waldenström macroglobulinemia

35.1 Title: Hereditary Neuropathies

Key Facts

- **Definition**
  Heritable genetic defects that affect selectively the peripheral nervous system (PNS) [myelin sheath, Schwann cell (SC), axon] or the PNS plus the central nervous system (CNS) and/or other organs [1]
- **Demographics**
  Rare disorders with prevalence less than 1:2000 when considered singly. All ages may be affected from birth to late adulthood.
- **Clinical features and terminology** (Table 35.1)
  (1) *Chronic length-dependent polyneuropathies*: hereditary motor-sensory neuropathies (alias CMT); distal hereditary motor neuropathies [(dHMN), alias spinal CMT or distal spinal muscular atrophy (dSMA)]; hereditary sensory and autonomic neuropathies (HSAN). (2) *Relapsing/progressive motor-sensory polyneuropathies* (Refsum disease). (3) *Chronic*, *progressive*, *motor-sensory polyneuropathies* with early small-fiber involvement (e.g., familial amyloid polyneuropathies). (4) *Painful neuropathies* (Fabry disease). (5) *Acute generalized polyneuropathies* (porphyrias). (6) *Chronic sensory neuronopathies* associated with hereditary ataxias. (7) *Chronic sensory* (and motor) neuropathies due to mitochondrial disorders [2]. *Recurrent focal neuropathies/plexopathies*: hereditary neuropathy with liability to pressure palsies (HNPP); hereditary neuralgic amyotrophy (HNA).
- **Diagnostic markers**
  - Clinical picture; neurophysiology; DNA testing; other laboratory tests in selected disorders: blood biochemical tests; MRI and or ultrasonography (US); CSF analysis; nerve biopsy.
- **Top differential diagnosis**
  Phenotypically convergent acquired neuropathies.
- **Prognosis**
  - **Principles of treatment** – Rehabilitation; symptomatic treatments (e.g., pain). Disease-modifying therapies available for selected forms, e.g., FAP (liver transplantation; pharmacotherapy; gene therapy); Fabry disease [Enzyme replacement therapy (ERT)]; acute intermittent porphyria [(AIP): hematine, glucose]; Refsum disease [diet; plasma exchange (PE); mitochondrial neurogastrointestinal encephalopathy [MNGIE: ERT, allogenic hematopoietic stem cell transplantation (HSCT)]. Disease-modifying therapies under investigation for many forms, e.g., CMT.
  - **Outcome and disability** – Variable, from minor disability throughout life (e.g., CMT) to relentless fatal course over years if untreated (e.g., FAP).

Table 35.1 Overview of hereditary neuropathies

Disease (inheritance)	Onset	PNS syndrome	Pathologal nerve process	Additional neurological features	Other signs	Laboratory tests	Therapy	Prognosis
CMT (AD, AR. X-l)	1st–2nd decade (birth-adult)	Chronic motor-sensory polyneuropathy	De-remyelinating or axonal or intermediate			DNA: >30 genes known	Rehabilitation ± othosis ± foot surgery	Variable spectrum of severity even within specific subtypes Typical: usually poorly and slowly progressive without relevant functional impairment Early onset: usually slowly progressive, with relevant functional impairment
dHMN (AD, AR. X-l)	1st–2nd decade (birth-adult)	Chronic distal motor neuropathy	Axonal	(± Pyramidal syndrome)		DNA: >10 genes known	Rehabilitation ± othosis ± foot surgery	Variable spectrum of severity even within specific subtypes Typical: usually poorly and slowly progressive without relevant functional impairment Early onset: usually slowly progressive, with relevant functional impairment
HSAN (AD, AR)	1st–2nd decade (birth-adult)	Chronic sensory (autonomic) neuropathy	Axonal			DNA: >10 genes known	HSAN1 (SPTLC1 mutations): oral L-serine	Usually progressive, morbidity and mortality variable within different subtypes
HNPP (AD)	1st–3rd decade (all decades)	Acute recurrent multifocal neuropathies	Demyelinating + tomacula			DNA (17p12 deletion or PMP22 mutations)	Rehabilitation ± othosis	Palsies may recur lasting for days to weeks (rarely months) usually without significant residual impairment Carriers may be asymptomatic
HNA (AD)	2nd–3rd decade (all decades)	Acute recurrent brachial (rarely lumbar) plexopathies	Axonal		Facial dysmorphisms	DNA: *SEPT9*e[)	Symptomatic treatment	Intense pain lasts for up two weeks and may result in chronic aching pain Long-term prognosis is favorable with functional recovery in more than 90 % patients after 4 years

(continue)

Table 35.1 (continue)

Disease (inheritance)	Onset	PNS syndrome	Pathologal nerve process	Additional neurological features	Other signs	Laboratory tests	Therapy	Prognosis
GAN (AR)	1st decade (typical: early childhood)	Motor-sensory polyneuropathy	Axonal, giant axons	Optic atrophy, nystagmus, cerebellar ataxia, pyramidal syndrome	Curled hair and eyelashes	DNA: *GAN* ± sural nerve biopsy	Rehabilitation ± othosis	Typical: slowly progressive with death by late adolescence
FAP (AD)	Adult, (from 3rd–4th to 7th decade)	Motor-sensory-autonomic polyneuropathy	Axonal, focal amyloid deposits	(± Leptomeningeal amyloidosis)	Weight loss, cardiomyopathy, vitreus opacity, nephropathy	DNA: *TTR* ± fat periumbilical and/or sural nerve biopsy	First-line: orthotopic liver transplantation Second-line: tafamidis, diflunisal, si-RNA, doxycycline + TUDCA Symptomatic treatment	Relentless progression if untreated with death 10–15 years after onset
Refsum (AR)	1st–5th decade (usually 1st–2nd)	Relapsing/remitting (or progressive) generalized polyneuropathy ± increased CSF proteins	Demyelinating	Pigmentary retinopathy, pupillary abnormalities, hearing loss, anosmia, cerebellar ataxia	Heart, skeletal deformities, ichthyosis, cataract	Blood: phytanic acid DNA: *PHYH*, *PEX7*	Dietary restriction (avoid phytol-containing fish oils, dairy products, ruminant fats) Plasma exchange for exacerbations	Early diagnosis and continuative treatment lead to significant restoration of neurological function but cranial nerve dysfunction does not regress
MLD (AR)	1st decade	Motor-sensory polyneuropathy	Demyelinating, metachromatic inclusions	Progressive psychomotor regression, dysarthria, aphasia, blindness, nistagmus, ataxia, spasticity		Brain NMR Blood: ARSA activity DNA: *ARSA* gene	HSCT	Usually fatal with variations depending on presentation's age (late-infantile, juvenile, adult)
KRABBE (AR)	1–2 years	Motor-sensory polyneuropathy	Demyelinating, globoid macrophages	Progressive psychomotor regression, blindness, ataxia, spasticity		Brain NMR Blood: GALC activity DNA: *GALC* gene ± sural nerve biopsy	HSCT	Early-infantile: fatal Late-onset slower progression with peripheral neuropathy and spasticity as the only manifestations

AMN (X-l)	2nd–3rd decade	Motor-sensory polyneuropathy	Axonal (± demyelination) CS lamellar inclusions	Spastic paraparesis	Adrenal insufficiency	Brain NMR Blood: VLCFA DNA: *ABCD1* gene	Dietary restriction of VLCFA; "Lorenzo's oil." Corticosteroid replacement	Slowly progressive
AIP (AD)	2nd decade-adulthood	Generalized acute polyneuropathy	Axonal	Psychosis, convulsions, coma, SIADH	Photosensitivity	Urine: ALA, PGB and stool: copro-/uroporphyrins Blood: PBG activity DNA: *PBG deaminase*	Prevention of acute attacks (be aware of precipitating drugs) For attacks: i.v. Glucose (10–20 g/h) or i.v. hematin 1–5 mg/kg/d for 3–5 days	Neuropathy improves with treatment Avoid precipitants factors
FABRY (X-l)	1st–2nd decade	Painful neuropathy	Axonal, small fibers Lamellated ultrastructural inclusions in perineurial, endothelial, perithelial cells	Strokes	Angiokeratoma, heart, kidney, corneal opacities, cataract	Brain NMR Blood: α-GLA activity DNA: *GLA*	ERT therapy is beneficial for nephropathy and pain control	Course is slowly progressive Death may occur by the 5th decade due to strokes or systemic complications
TANGIER (AR)	2nd decade-adulthood	Pseudo-syringomyelic syndrome (or multifocal mononeuropathies)	Axonal, small fibers (demyelination) CS lipid vacuoles		Large orange tonsils, ischemic cardiomyopathy, corneal opacity, hepatosplenomegaly, decreased cholesterol and HDL levels	Blood: cholesterol, VLDL DNA: *ABC1*	Specific treatment unavailable	Progressive course influenced by systemic complications (premature myocardial infarction (30 % of cases), stroke, thrombocytopenia
FRIEDREICH (AR)	1st–2nd decade	Sensory neuronopathy	Axonal, no clusters of regenerating fibers	Pyramidalism, dysarthria, nistagmus	Cardiomyopathy, diabetes (consider diabetes neuropathy) Skeletal deformities	DNA: *FRDA*	No proven effective disease modifying therapies. Idebenone is given to slow progression of cardiomyopathy	Relentless progressive Cardiomyopathy is a frequent cause of premature mortality Several therapeutic strategies under investigation

(continue)

Table 35.1 (continue)

Disease (inheritance)	Onset	PNS syndrome	Pathologal nerve process	Additional neurological features	Other signs	Laboratory tests	Therapy	Prognosis
Ataxia-Vitamin E Deficit (AR)	1st–2nd decade	Sensory neuronopathy	See above		Cardiomyopathy, diabetes Skeletal deformities Retinitis pigmentosa	Blood: vitamin E DNA: *TTPA* gene	Treatment with vitamin E slow progression	Onset (childhood or adult) and natural history influenced by residual TTP activity
ABETA-LYPO Proteinemia (AR)	1–2 decade	Sensory neuronopathy	See above		Retinitis pigmentosa, acanthocytosis, malabsorption, hypocholesterolemia deficits, liposoluble vitamins	Blood: vitamin E, cholesterol, acanthocytosis DNA: *MTP*		Slowly progressive
MNGIE (AR)	1st decade-adulthood	Chronic motor-sensory CIDP or CMT1-like evolution and features	Demyelinating	± ptosis, ophthalmoparesis, leukoencephalopathy Myopathy with RRF, mtDNA deletion and/or depletion	Severe gastrointestinal dysmotility (pseudo-obstruction), cachexia	Blood: reduced TYMP activity; increased urinary and plasma dThd, dUrd DNA: TYMP mutations. Muscle: RRF and COX-fibers, mtDNA deletions	Continuous peritoneal dialysis. HSCT Erythrocyte-entrapped enzymatic therapy Platelet infusion Caution with liver primary metabolizing drugs	Variable from rapid, often lethal course between 20–40 years to late-onset and slower forms [2]
SANDO/ SCAE (AR)	Juvenile-to-adult	Sensory neuronopathy	Axonopathy or axonal-demyelinating	± dysarthria, ophthalmoparesis Hearing loss, migraine, myopathy with RRF and mtDNA depletion		DNA: *POLG DNA*: *C10ORF72*		POLG1: moderate-to-severe C10ORF72: mild or subclinical, rarely severe
NARP (matrilinear mtDNA)	1–3 decade	Sensory neuronopathy	Axonopathy (may be the unique feature)	± epilepsy	Retinitis pigmentosa Developmental delay	DNA: mtDNAATP6		Moderate to severe

CMT Charcot-Marie-Tooth, *dHMN* distal hereditary motor neuropathy, *HSAN* hereditary sensory-autonomic neuropathy, *HNPP* hereditary neuropathy with liability to pressure palsies, *HNA* hereditary neuralgic amyotrophy, *GAN* giant axonal neuropathy, *FAP* familial amyloidotic polyneuropathy, *MLD* metachromatic leukodystrophy, *AMN* adrenomyeloneuropathy, *AIP* acute intermittent porphyria, *SANDO* sensory ataxic neuropathy, dysarthria, ophthalmoparesis, *SCAE* spinocerebellar ataxia and epilepsy, *MNGIE* mitochondrial neurogastrointestinal encephalopathy, *NARP* neurogenic muscle weakness, ataxia, retinitis pigmentosa, *AD* autosomal dominant, *AR* autosomal recessive, *X-l* X–linked, *SIADH* syndrome of inappropriate ADH secretion, *RRF* ragged-red fibers, *SEPT9* septin 9, *GAN* gigaxonina, *TTR* trasntiretina, *PHYH* phytanoyl-CoA 2-hydroxylase, *PEX7* peroxisome biogenesis factor 7, *ARSA* arylsulfatase A, *GALC* galactosylceramidase, *VLCFA* very-long-chain fatty acids, *ABCD1* ATPase-binding cassette-D1, *ALA* acido δ-aminolevulinico, *PBG* porfobilinogeno, *GLA* a-galactosidade A, *ABC1* ATP-binding cassette transporter 1, *FRDA* Friedreich ataxia gene, *TTPA* α-tocopherol transfer protein, *MTP* microsomal triglyceride transfer protein, *POLG* DNA polymerase gamma, *mtDNA* mitochondrial DNA, *ATP6* ATP synthase subunit 6, *HSCT* allogenic hematopoietic stem-cell transplantation, *ERT* enzyme replacement therapy

35.1.1 Charcot-Marie-Tooth Disease (CMT)

35.1.1.1 Terminology

Alias: Hereditary Motor and Sensory Neuropathy (HMSN) or peroneal muscular atrophy.

35.1.1.2 Demographics

The most frequent hereditary neuromuscular disorder with a general prevalence of about 1:2500. All modes of Mendelian inheritance are possible. In most European and US populations, 90 % of cases are autosomal dominant or X-dominant (CMTX), while 10 % are autosomal recessive. Autosomal dominant CMT: demyelinating subtypes (CMT1) more common (60 %) than the axonal subtypes (CMT2) (40 %), but the true prevalence of CMT2 is unknown and approximately 70 % of the CMT2 genes remain unidentified [3].

35.1.1.3 Clinical Features

Common Phenotype associated to CMT1, CMTX, and CMT2: onset in infancy or childhood, difficulty in running, twisting of ankles, pes cavus (planus at onset) and hammertoes, progressive peroneal atrophy with steppage gait, foot drop, mild sensory ataxia, weakness/wasting of hand intrinsic muscles, stocking-glove multimodal sensory loss.

Clinical clues: positive family history, presentation in the first-second decade, long and slow progression, foot deformities, paucity of positive sensory symptoms, degree of functional impairment milder than neurophysiological involvement. Postural tremor may be prominent independently of genetic subtypes (Roussy-Lévy syndrome).

Caveats: truly isolated cases may occur, caused by de novo dominant mutations. Dominant forms may be associated to age-independent intrafamilial phenotypical variability, from asymptomatic to severe disease. CMTX may be suggested by pedigree analysis (no male-to-male transmission; males affected, females asymptomatic or mildly affected) but a few CMTX females may be severely affected.

Early-Infantile Phenotype with perinatal onset, hypotonia, and breathing difficulties, or with delay of motor milestones. Severe weakness and wasting of distal and proximal muscles, sensory ataxia, foot and spine deformities, possible cranial involvement (mild ophthalmoparesis, facial weakness, neurosensorial hearing loss, vocal cord paralysis). Inheritance may be autosomal dominant with most cases isolated due to de novo mutations (demyelinating CMT3 alias Dejerine-Sottas disease), or autosomal recessive (demyelinating CMT4, or axonal AR-CMT2).

Adult Onset Phenotype Associated to CMT1B, CMTX women, CMT2. Symptoms develop after 40–50 years.

Special phenotypes CMTX may be suggested by marked involvement of abductor pollicis brevis; exceptional CMTX cases may present acute transitory leukoencephalopathies. Adult onset CMT2 may be associated with pupillary abnormalities, hearing loss and/or paresthesias/pain (CMT2I/J). CMT2 may be associated with optic neuritis/optic atrophy (CMT2-VI) or with brisk reflexes in the upper and proximal lower limbs (CMT2-V). Some genetic subtypes of CMT2 have a prevalent motor (CMT2F) or sensory involvement (CMT2B) that may affect prevalently the arms (CMT2D), or cause vocal cord paralysis (CMT2C).

35.1.1.4 Diagnostic Markers

Blood No biochemical markers available.

DNA Causal genes have been increasingly identified (more than 50 genes known, updated database at http://www.molgen.ua.ac.be/CMTMutations/). Many genes are tested currently by Sanger sequencing using a single-gene approach based on mutational frequencies; high throughput mutational analysis done by next-generation-sequencing techniques is becoming available for diagnostic purposes. Approximately 80–90 % of CMT1 have the duplication of chromosome 17p12 (*PMP22* gene), the remaining have mutations (mostly point mutations) in *GJB1*/*Cx32* (CMT1X, 6–20 %), *MPZ*/*P0*

(CMT1B, 5 %), *EGR2*, *PMP22*, *LITAF*/*SIMPLE*. Only 25–30 % of CMT2 receive a molecular diagnosis having mutations of *MFN2* (CMT2A, 10–20 % of all cases), *GJB1*/*Cx32* (CMTX), *MPZ*/*P0* (CMT2J), *NEFL* (CMT2E), *GDAP1* (CMT2K), *HSPB1* (CMT2F), *TRPV4* (CMT2C), *GARS* (CMT2D), or even other rarer genes. Dominant intermediate CMT is most frequently reported to be associated with *GJB1* (CMTX), *NEFL* (CMT2E), and *DNM2* (CMT2M). Autosomal recessive CMT is most frequently associated with mutation of *SH3TC2* (CMT4C, early, prominent kyphoscoliosis), *GDAP1* (CMT4A, AR-CMT2, AR- CMT intermediate), *HINT1* (predominant motor ± neuromyotonia).

CSF Is not analyzed with exception of the differential diagnosis with acquired neuropathies, when molecular investigations are negative, or for the diagnosis of an acquired disorder superimposed onto a known genetic neuropathy. Mildly increased protein content is occasionally found in CMT1 and CMT3, without any clear-cut boundary levels with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Imaging In CMT1-CMT3 inversion recovery (STIR)-MRI neurography may disclose hypertrophy ± MRI contrast enhancement of spinal roots, cauda equina, plexuses and/of median and ulnar nerves; ultrasound (US) discloses marked and diffuse increase of the cross-sectional area (CSA).

Neurophysiology Autosomal dominant CMT1 and CMT3, and autosomal recessive CMT4: uniformly slow nerve conduction velocities (NCV) with median and ulnar motor NCV (MNCV) < 38 m/s (below 12 m/s in CMT3) and proportionate delay in distal motor latencies and F-wave latencies. There is a relative preservation of CMAP while SAP decreases or is absent. In CMT1, NCV changes are fully penetrant independently of the clinical status. Autosomal dominant CMT2 and autosomal recessive AR-CMT2: NCV is preserved or mildly decreased (usually median or ulnar MNCV > 38 m/s), while CMAP and SAP are reduced. In CMT2, the electrodiagnostic changes may have incomplete penetrance. CMT1X male and rare autosomal dominant intermediate DI-CMT: median or ulnar MNCV between 25 and 45 m/s; MNCV is normal or slightly reduced in CMT1X women. In CMT1X, nerve conduction abnormalities may be non-uniform between and within nerve trunks with excessive temporal dispersion and conduction blocks.

35.1.1.5 Pathology

A sural nerve biopsy is no longer indicated unless for a differential diagnosis with other inherited neuropathies or with various, eventually superimposed, acquired neuropathies.

Besides demonstrating hypertrophic de-remyelination (CMT1, CMT4), hypo-amyelination (CMT3), or a chronic axonal neuropathy (CMT2), nerve biopsy may disclose additional pathological abnormalities of peculiar genetic forms: outfoldings and myelin uncompaction in CMT1B; prominent myelin outfoldings and/or basal-lamina SC onion bulbs in some CMT4 subtypes; giant axons in CMT2E.

35.1.1.6 Top Differential Diagnoses

CMT1: CIDP, anti-MAG neuropathy, familial amyloid polyneuropathies (FAP).
CMT3: metachromatic leukodystrophy, hereditary ataxias, Refsum disease, mitochondrial encephalomyopathies (MNGIE).
CMT2: acquired axonal neuropathies, FAP, distal myopathy, dHMN, HSAN, spinal dysraphism, mitochondrial encephalomyopathies (MNGIE, POLG1 mutations), GAN.
CMT5: hereditary spastic paraplegias (HSP).

35.1.1.7 Therapy

There are no specific medical therapies for any of the genetic subtypes. Treatment is supportive with rehabilitation and orthotics. Mild-to-moderate exercise is safe and likely effective. Effects of high-resistance training are controversial because it could result in overwork-weakness. Passive stretching is advised to prevent and counteract tendon retractions. Plantar and/or custom-fitted

ankle-foot orthoses are prescribed to correct foot position and to overcome foot drop.

Different surgical interventions for foot deformities.

Symptomatic therapy of neuropathic pain, joint/bone pain, paresthesias, cramps, fatigue, and restless leg syndrome is done as for other neuropathies.

35.1.1.8 Prognosis

Genetic counseling of probands and families is mandatory for diagnostic, predictive, prenatal, and pre-implantation testing.

Independently of the primary demyelinating or axonal process, evolution is associated with axonal loss. CMT-neuropathy score (CMT-NS), a composite clinical and neurophysiological score, is a validated tool for natural-history studies; patients are classified as mild (≤10), moderate (11–20), or severe (>20); in CMT1A the mean annual progression is 0.69 points/year. Most patients with CMT1A and CMT1X do not require ambulation aids beyond ankle-foot orthoses. CMT3 patients may require above-the-knee bracing, walkers, or wheelchairs by 20 years of age.

Periods of self-limiting worsenings may be related to growth in childhood and adolescence. Acute or subacute worsenings should prompt to exclude a superimposed, treatable, acquired neuropathy (e.g., GBS, CIDP, diabetic neuropathy).

Guillain-Barré syndrome or GBS-like syndromes have been reported after chemotherapy; cancer in CMT should be treated with less neurotoxic chemotherapeutic agents.

Some patients report faster deterioration during pregnancy, usually but not always, with recovery.

Anesthetics are well tolerated but regional anesthesias are considered somewhat contraindicated.

35.1.2 Hereditary Neuropathy with Liability to Pressure Palsy (HNPP)

35.1.2.1 Terminology and Definitions

HNPP (alias tomaculous neuropathy) is an autosomal dominant demyelinating polyneuropathy manifesting most frequently with acute/subacute painless palsies at common entrapment sites, caused by haploinsufficiency of *PMP22* (commonly associated to the 1.4 Mb deletion of chromosome 17p12).

35.1.2.2 Demographics

Prevalence is theoretically similar to CMT1A. Up to 25 % of the carriers of the 17p12 deletion may be asymptomatic, having a subclinical polyneuropathy. All ages are involved; the first episode is usually in the second-third decade, occasionally in childhood.

35.1.2.3 Clinical Features

Typical Presentation (Approximately Two-Thirds of Patients) episodic, painless, recurrent focal, and motor palsies affecting variably the median, ulnar, peroneal nerves or brachial plexus often preceded by minor compression or trauma at vulnerable sites (wrist, elbow, knee, shoulder). Palsies may be debilitating and last for days or weeks (or rarely months). Besides episodes, patients often complain of positional acroparesthesias and disclose reduced or absent deep tendon reflexes and mild pes cavus.

Atypical Presentations may occur in up 30 % of patients and include: chronic sensory polyneuropathies, CMT1-like polyneuropathies, chronic ulnar neuropathies, acute syndromes with multiple limbs involved, carpal tunnel syndromes.

35.1.2.4 Pathophysiology

Haploinsufficiency associated to the common deletion of *PMP22* (90–95 % of cases) or to rare micromutations cause a mild chronic demyelinating polyneuropathy marked by sausage-like "tomaculous" focal thickenings of the myelin sheath. Focal constrictions of axons segments enclosed by tomacula may predispose to mechanically induced CB and acute clinical deficits.

35.1.2.5 Diagnostic Markers

Blood DNA The most common molecular lesion is the 1.4 Mb 17p12 (*PMP22*) deletion. A minority

of cases (approximately 5 %) have micromutations of *PMP22* (nonsense or frameshifting mutations).

Imaging US may disclose nerve enlargements at multiple sites of entrapment but its sensitivity and specificity is still limited.

Neurophysiology Neurophysiological testing provides a reliable picture even in asymptomatic cases. Distal motor latencies (DML) are prolonged in median, ulnar nerves, and peroneal nerves with only mild slowing in the distal segments (median MNCV usually above 38 m/s); SAPs are diffusely reduced; coNduction blocks CB over entrapment sites are characteristic in symptomatic nerves.

35.1.2.6 Pathology

Sural nerve biopsy has full specificity and almost complete sensitivity but is no longer indicated. It discloses a chronic demyelinating polyneuropathy with a variable number of *tomacula* (sausage-like myelin thickenings) in semithin and ultrathin sections and in teased fibers.

35.1.2.7 Top Differential Diagnoses

Entrapment neuropathies. Vasculitic neuropathies. Familial carpal tunnel syndrome (CTS). Idiopathic and hereditary neuralgic amyotrophy (HNA).

HNA is an autosomal dominant disorder caused by mutations or intragenic duplications of the septin 9 (*SEPT9*) gene that manifests with recurrent attacks of pain, weakness, and sensory disturbance with predilection for the brachial plexus. It progresses 2–3 weeks after the onset of pain and involves, in some cases, the phrenic nerves and/or cranial nerves VII and X. Associated features include: short stature, hypotelorism, long nasal bridge, cleft palate, epicanthal folds, facial asymmetry, and partial syndactyly. HNA may develop in all ages (most commonly in the second-third decade), possibly triggered by periods of physical (partum), immunological, or emotional stress.

35.1.2.8 Prognosis and Therapy

Management is mainly preventive: employment or recreational activities which increase the risk of nerve compression should be avoided. Obstetricians and surgeons should be informed of the diagnosis, to avoid prolonged positioning of the body and limbs. Peripheral regional anesthesia is somewhat contraindicated. Surgery is sometimes offered for nerve entrapment release but any benefit tends to be short-lived.

Life expectancy is normal and most patients have a good quality of life. About 10 % of patients make an incomplete recovery from episodes of nerve palsy due to persistent CBs. Age-related irreversible motor axonal damage may ensue at entrapment sites [4].

Management is mainly preventive: employments or recreational activities with increased risk of nerve compression should be avoided. Obstetricians and surgeons should be informed of the diagnosis to avoid prolonged positioning of the body and limbs.

35.1.3 Familial Amyloid Polyneuropathies (FAP)

35.1.3.1 Terminology and Definitions

Autosomal dominant disorders associated with the extracellular deposition of amyloid fibrils made of the mutated proteins: transthyretin (TTR), apolipoprotein A1 (APOA1), or gelsolin (GSN). TTR is a plasma transporter for thyroxine and vitamin A produced predominantly by liver.

35.1.3.2 Demographics

TTR-FAP variants are world widely distributed: incidence in the USA is 1:100,000 individuals; the Val30Met variant is endemic in some areas of northern Portugal (incidence 1 in 538 individuals), northern Sweden, Japan, and Brazil. GSN-FAP has some clusters in southeastern Finland and it is very rare in other European countries, USA, and Japan. APOA1-FAP, described in an Iowa kindred with British extraction, was also reported in rare families with different ancestries [5].

35.1.3.3 Clinical Features

TTR-FAP Val30Met in endemic areas: onset in third-fourth decade, relentless sensory-motor-

autonomic polyneuropathy with superimposed CTS, cardiac and kidney dysfunction.

Clues to diagnosis: stabbing lancinating pain, gastrointestinal motility disturbances, erectile dysfunction, orthostatic hypotension, neurogenic bladder, bulbar involvement, cardiomyopathy with thickened ventricular walls, advanced atrioventricular block, cotton-wool inclusions of vitreous body, glaucoma, albuminuria, hyperazotemia.

Val30Met in non-endemic areas and other molecular variants: reduced penetrance (less than 50 %), later adult onset (up to seventh decade, mean age 55–60 years), lack of familiarity, CIDP or *Amyotrophic Lateral Sclerosis* (ALS)-like evolution with fasciculations, lack of pain or dysautonomia, much later multi-system involvement, isolated CTS preceding polyneuropathy of several years. A minority of TTR mutations may lead to selective oculo-leptomeningeal amyloidosis (stroke, seizures, hydrocephalus, spinal cord infarction, vitreous opacities) or cardiac amyloidosis (restrictive cardiomyopathy).

GSN-FAP Onset in third-fourth decades. Corneal lattice dystrophy, multiple cranial neuropathies (facial and bulbar weakness), cutis laxa. Late generalized polyneuropathy. Symptoms generally worsen with age.

APOA1-FAP Onset in the third-fourth decades. Painful, autonomic, sensorimotor polyneuropathy. Early renal involvement, peptic ulcer disease.

35.1.3.4 Diagnosis

In non-endemic areas the mean interval from onset to diagnosis of TTR-FAP is 3–4 years.

35.1.3.5 Laboratory

Blood DNA Mutational analysis of involved genes.

CSF Analysis is not indicated; when done may be misleading revealing an increased protein content.

Blood *TTR-FAP* Some serum variants of TTR may be detected by mass spectrometry (not routinely); plasma NT-proBNP, high sensitivity troponin, creatinine clearance and albuminuria (for evaluating cardiac and renal progression).

Neurophysiology *TTR-FAP*: NCV studies consistent with an axonal polyneuropathy ± CTS, sometimes with a demyelinating polyneuropathy [6]. EMG: denervation. Autonomic tests: sympathetic skin reflex, quantitative sensory testing (QST), beat-to-beat heart rate variability (HRV: ECG rate monitoring while breathing in-and-out at six breaths per minute).

ECG and Two-Dimensional Echocardiography *TTR-FAP*: cardiac assessment and non-invasive diagnosis of amyloidotic cardiomyopathy.

Imaging *TTR-FAP*: *cardiac magnetic resonance* (delayed gadolinium enhancement to detect amyloid in the myocardial interstitium).

Scintigraphy with ^{99m}Tc-DPD to image amyloid in the myocardium. Scintigraphy with ^{123}I-MIBG to reveal loss of sympathetic nerve endings in heart. Scintigraphy with ^{123}I-SAP to evaluate extent and distribution of amyloid deposits in soft tissues and visceral organs except heart.

Biopsies *TTR-FAP*: demonstration of amyloid deposits by Congo red staining (green birefringence under polarized light) and electron microscopy is essential for eligibility for liver transplantation. Sensitivity is as follows: subcutaneous fat approximately 60 % (repeatable); sural nerve or gastrointestinal mucosa approximately 80 %. Immunohistochemistry with anti-TTR antibodies is mandatory to characterize the biochemical nature of the amyloid fibrils. Liquid chromatography-tandem mass spectrometry may also identify precursor proteins of amyloid fibrils, including variant TTR.

35.1.3.6 Top Differential Diagnoses

TTR-FAP AL (amyloid light chain)-amyloidosis. Diabetic, alcoholic neuropathies. CIDP. Paraneoplastic neuropathies. CMT2. Fabry disease. ALS.

35.1.3.7 Therapy

Disease-Modifying Treatments

Orthotopic liver transplantation (OLT) is the first line therapy, removing approximately 95 % of mutant blood TTR. OLT is indicated in early stages with bioptically proven amyloidosis [7]; [see also Familial Amyloidotic Polyneuropathy world Transplant Registry and Domino Liver Transplant Registry (www.fapwtr.org)].

Life expectancy is better in Val30Met patients (10-year survival approximately 74 % compared with 44 % in non-Val30Met patients), in patients transplanted earlier in the disease, in patients <50 years. Low modified body mass index (<600) is a negative predictor. Besides life expectancy, some Val30Met patients reported improvement of gastrointestinal, autonomic, peripheral-nerve symptoms, but recovery of nerve function does not occur. Patients in later stages and some non-Val30Met patients disclose progression after transplantation due to continued deposition of wild type TTR and/or of the mutant TTR in heart (progressive restrictive cardiomyopathy, cardiac autonomic denervation) and PNS.

OLT is not indicated in predominantly leptomeningeal amyloidosis.

Combined heart and liver transplant is indicated in severe heart failure due to amyloidotic cardiomyopathy in patients without advanced neurologic involvement. Liver transplant is also an option for non-Val30Met candidates with echocardiographic evidence of cardiomyopathy.

Domino liver transplant of FAP-livers in patients with liver failure is an accepted procedure but it may lead to TTR-FAP in the recipients after 8–10 years.

The following pharmacotherapies are a second line option for patients not eligible for OLT or waiting for OLT in early stages of disease [8]: kinetic stabilizers (tafamidis, authorized for marketing in Europe for early stages of disease; diflunisal); fibril disruptors (oxycycline/tauroursodeoxycholic acid). Gene-therapy approaches are becoming available including antisense oligonucleotides (ASO) and RNA interference-based molecules vehicled by lipid nanoparticles.

Symptomatic Treatments

Neuropathic pain (see Chap. 40) and autonomic dysfunction are treated as in other neuropathies (see Chap. 36).

35.1.3.8 Prognosis

TTR-FAP is relentlessly progressive. Untreated patients with the classical Portuguese phenotype die 10–15 years after onset because of malnutrition, cardiac or renal failure, or cardiac arrhythmias (Transthyretin Amyloidosis Outcomes Survey –THAOS – www.thaos.net).

Follow-up should be done every 6 months including neurological disability scores, full neurophysiological and cardiological laboratory tests, and evaluation of the modified body mass index (BMI) (BMI multiplied by serum albumin level). Degrees of clinical involvement: 0 = no symptoms, variant TTR form, evidence of amyloid deposits; I = unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs; III = assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk; III = wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs.

35.1.4 Porphiric Neuropathy

35.1.4.1 Terminology and Definitions

Acute neuropathy resembling Guillain-Barré syndrome (GBS), associated to dysfunction of the autonomic and central nervous systems. Neuropathic porphyrias are caused by the following autosomal dominant enzymatic defects in the hepatic biosynthesis of heme: porphobilinogen (PBG) deaminase (acute intermittent porphyria – AIP); copro oxidase (hereditary coproporphyria – HCP); proto oxidase (variegate porphyria – VP).

35.1.4.2 Demographics

Carriers of the genetic defect are estimated to be 1/80.000 people; prevalence was 20-times higher in the psychiatric hospital populations in the USA. Ten to forty percent of carriers may develop neuropathy. Attacks are five times more frequent

in women and manifest usually in the third and fourth decades.

35.1.4.3 Pathophysiology

Predominantly proximal motor axonal damage with Wallerian degeneration and secondary demyelination. Peripheral and central neuronal involvement might result from impaired energy metabolism due to heme deficiency and/or toxicity by the common precursor δ-aminolevulinic acid (ALA).

35.1.4.4 Clinical Features

Acute attacks are often triggered by fasting, porphyrinogenic treatments (estrogen/progesterone contraceptives, barbiturates, sulfonamides, antiepileptics, any drug that is metabolized by the P450 system), sepsis or alcohol (possibly misinterpreted as acute intoxication). Attacks feature the classic triad of abdominal pain, psychosis, and neuropathy. They manifest as an autonomic neuropathy (resting tachycardia, papillary abnormalities, abdominal pain, nausea, vomiting, and severe constipation mimicking a surgical abdomen) and neuropsychiatric changes (anxiety, insomnia, seizures, hallucinations, sudden changes in behavior; the recurrence during the luteal phase may be misdiagnosed as a bipolar disorder). Motor neuropathy manifests subacutely 3–75 after onset (within 1 month in 80 % of cases) and progresses symmetrically for over 1 month; at nadir total quadriplegia and respiratory insufficiency may ensue requiring ventilatory support; facial and bulbar weakness are common. Evolution may be descendent from arms to legs with rapid muscle wasting. Sensory symptoms may be associated or not to distal sensory loss; tendon reflexes are diminished or absent, rarely retained. Atypical presentations include progressive motor neuropathies, mostly affecting the upper limbs, without abdominal pain.

Patients with HCP and VP may develop cutaneous photosensitivity in adult life.

35.1.4.5 Top Differential Diagnosis

GBS, vasculitis, heavy metal intoxication, poliomyelitis.

35.1.4.6 Diagnostic Markers

CSF Proteins can be normal or mildly elevated.

Blood and Urine The diagnosis of porphiric attack is made revealing a marked elevation of PBG and ALA in blood, urine, and stool. During an attack, urine may be brown reflecting high concentration of porphyrin metabolites. Enzymatic assays may identify and distinguish among hepatic porphyrias, but the results may be misleading.

Neurophysiology NCV studies show an axonal neuropathy with decreased amplitudes of motor responses and possible slowing of conduction velocities secondary to large-fiber loss, without CB or abnormal temporal dispersion; sensory function is relatively or completely spared. EMG demonstrates prominent fibrillation potentials within weeks of onset, most prominent in proximal muscles.

35.1.4.7 Prognosis and Therapies

Once aborted, the prognosis of a single attack is generally good with rapid resolution of the autonomic and psychiatric symptoms. Recovery of neuropathy is slower, often occurring over many months (approximately 10 months for proximal muscles and 20 for distal muscles), usually with incomplete recovery. Sixty-eighty percent of patients have a single acute attack of porphyria. Since cumulative fixed deficits may ensue after repeated attacks, the long-term prognosis depends on successful prevention of attacks.

The prognosis of AIP is good even in severe, acute attacks. Anyway, AIP carries a potentiality fatal outcome due to motor and autonomic involvement with respiratory and bulbar paralysis and/or cardiac arrhythmias.

Prevention is based by awareness and avoidance of precipitating drugs and situations. During an attack abortive therapies include IV glucose (10–20 g/h) followed, if there is no improvement, by IV hematin (1–5 mg/kg/day infused over 30–60 min); supportive therapies are discussed in the following section of GBS. **

35.2 Title: Immunomediated Neuropathies

Key Facts

- **Terminology and definitions**
  - **Acute forms** – *GBS*: acute inflammatory polyradiculoneuropathies reaching their maximal severity within 4 weeks. Variants AIDP, AMAN, acute motor-conduction-block neuropathy, AMSAN, acute sensory neuronopathy, MFS, GBS-MFS overlaps, acute panautonomic neuropathy. *MFS*: acute ataxia, with ophthalmoplegia and areflexia.
  - **Chronic forms** *CIDP* = Acquired demyelinating neuropathy reaching maximal severity in at least 8 weeks.:
  - *MMN* = Peripheral neuropathy with slowly progressive or remitting asymmetric distal weakness and persistent motor conduction blocks, without significant sensory loss.
- **Clinical features**
  - **Acute forms** – Incidence: 1.8/100,000 for *GBS*; 0.1/100,000 for *MFS*. Gastrointestinal or respiratory upper-tract infection before onset in 66 % of patients. Progressive weakness of both legs and arms with areflexia characterize AIDP, AMSANm AMAN. In *MFS* ophthalmoparesis may develop asymmetrically but often becomes complete; pupillary involvement is uncommon.
  - **Chronic forms** – *CIDP* prevalence: 1.97–4.77/100,000. Typical forms (80 % of cases) are characterized by symmetrical distal and proximal weakness, sensory loss and paresthesias, absent deep tendon reflexes with progressive or relapsing/remitting course. *MMN* prevalence: 1–2/100,000. MMN show weakness developing over months or years with a multifocal asymmetric distribution in individual nerves and usually prominent in the distal arms.
- **Diagnostic markers**
  - **Blood** – Ig auto-Ab anti-GM1 in: *AMAN*, *AMSAN*, and acute motor-conduction-block neuropathy. *MFS*: Ab anti-GQ1b in 95 % of patients.
  - **MMN** – IgM auto-Ab anti-GM1 in 40–50 % of patients.
    - **CSF** – Albumin-cytologic dissociation. Normal in MMN.
    - **MRI** – Possible enhancement and/or hypertrophy of the cauda equina, lumbosacral nerve roots, brachial and lumbosacral plexuses.
    - **Neurophysiology** – Demyelination and CBs in *AIDP* and *CIDP*; axonopathy in *AMAN*.
- **Top Differential Diagnoses**
  - **Acute forms** – Polymyositis, myasthenia gravis, CIDP. *MFS*: Brainstem ischemia, Wernicke's encephalopathy.
  - **Chronic form***s* – *CIDP*: Polyneuropathies of different cause; Myopathies.
  - **MMN**: Motor neuron disorders. CIDP. Myopathies.
- **Prognosis and Principles of treatment**
  - **Acute forms** – PE or IVIg within the first 2–4 weeks from onset.
  - **Chronic forms** – *CIDP*: Steroids, PE and IVIg. *MMN*: IgIV are effective in 79–86 % of patients. Steroids are contraindicated in MMN.
- **Disability**
  - **Acute forms** – *GBS*: 5 % of patients die, 5–10 % remain disabled or severely fatigued, 15 % are asymptomatic 1–2 years after onset. *MFS*: mostly benign. Recovery takes a median of 1–3 months. By 6 months, most patients are free from ataxia and ophthalmoparesis.
  - **Chronic forms** – *CIDP*: age <45 years predicts a better outcome; axonal loss is associated with poorer prognosis. In the long term, mortality ranges from 1.3 to 9 %; 40 % of patients have no or non-disabling symptoms, 75 % are able to work, 24 % carry severe handicap.
  - **MMN**: very uncommon spontaneous remissions. In the long term, 1/3 of patients improves, 1/3 is IgG dependent, and 1/3 continues to be non-responsive.

35.2.1 Guillain-Barré Syndrome (GBS)

35.2.1.1 Definition and Terminology

GBS is an acute, inflammatory, areflexic paralysis with variable degree of weakness that reaches maximal severity within 4 weeks, usually with an ascending progression from lower to upper limbs and cranial nerves, and albuminocytologic dissociation [9].

Clinical and/or electrophysiological variants:

1. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
2. Acute motor axonal neuropathy (AMAN)
3. Acute motor-conduction-block neuropathy
4. Acute motor-sensory axonal neuropathy (AMSAN)
5. Acute sensory neuronopathy
6. Miller-Fisher syndrome (MFS)

7. GBS-MFS overlaps
8. Acute panautonomic neuropathy

35.2.1.2 Demographics

Worldwide mean annual incidence is 1.8 per 100,000 for GBS (ranging from 0.8 for age <18 years to 3.2 for age >60 years) and 0.1 per 100,000 for MFS. Males are affected more frequently than females (1.5:1). AIDP accounts for 90 % of cases in North America and Europe; AMAN accounts for 30–47 % of cases in Asia and Central and South America and 5 % of cases in Western countries. AIDP is non-seasonal; AMAN may occur in summer epidemics in northern China affecting children and young adults and is likely associated with *Campylobacter* (*C.*) *jejuni* infections.

Two-thirds of patients report an event 1–4 weeks before onset, most frequently symptoms or signs of gastrointestinal or respiratory upper-tract infection: *C. jejuni* (30 %), cytomegalovirus (CMV) (10 %), Epstein-Barr virus, Varicella-zoster virus, HIV, *Mycoplasma pneumoniae*, *Haemophilus influenzae*.

Incidence of GBS is 0.25–0.65 per 1000 cases of *C. jejuni* infection and 0.6–2.2 per 1000 cases of primary CMV infection. Less frequent antecedents: vaccinations (only brain-derived rabies vaccines have been associated with elevated risk above the background incidence), drugs (heroin, streptokinase, suramin, gangliosides), or surgical procedures.

35.2.1.3 Pathophysiology

Immune-mediated disorders resulting from generation of autoimmune antibodies and/or inflammatory cells which cross-react with epitopes on peripheral nerves and roots, leading to demyelination or axonal damage or both. Molecular mimicry may involve ganglioside epitopes of myelin (AIDP) or axonal membranes (AMAN) and lipopolysaccharide epitopes of infectious agents. Antiganglioside antibodies that cross-react with *C. jejuni* are common in AMAN and AMSAN (anti-GM1 in 65 % of patients); MFS (anti-GQ1b in more than 90 % of patients) and acute sensory neuronopathy (anti-GD1B).

In AIDP anti-myelin antibodies directed against epitopes on the abaxonal SC membrane may lead to demyelination with activation of complement and recruitment of macrophages, followed by secondary axonal degeneration. In AMAN anti-GM1 antibodies react against epitopes at nodes of Ranvier and along the axolemma of motor fibers; activation of complement and recruited macrophages lead to Wallerian degeneration.

35.2.1.4 Diagnosis

Diagnosis is based on clinical characteristics and ancillary laboratory investigations [10]. New criteria to better identify patients for vaccine safety studies are under validation [11].

Clinical Criteria

AIDP Required features: progressive weakness of both legs and arms; areflexia. Supportive features: progression over days to 4 weeks (more often with ascending evolution); relative symmetry of symptoms and signs; mild sensory symptoms or signs (distally decreased vibration sense); moderate-severe pain in extremities, interscapular area or back (in up 89 % of patients in the acute phase); bifacial palsies (45–75 % of patients, whereas involvement of extraocular muscles and lower cranial nerve is less common); autonomic instability (in up to 65 % of patients); monophasic evolution pattern with recovery beginning 2–4 weeks after progression ceases.

AMSAN and AMAN overlap clinically with AIDP (AMAN have non-sensory signs or symptoms) but diverge in electrodiagnostic features and prognosis.

35.2.1.5 Diagnostic Markers

Supportive Criteria

CSF elevated protein with <10 cells/μl in 80 % of patients after 2 weeks (pleocytosis >10 lymphocytes/μl should prompt to consider Lyme disease, recent HIV infection, sarcoidosis, and poliomyelitis).

Neurophysiology Electrodiagnostic (EDX) is aimed at detecting signs of multifocal demyelination (AIDP) or axonopathy (AMAN), showing signs of polyneuropathy in the arms when weakness is only in the legs, excluding other diagnoses.

AIDP EDX criteria are at least one of the following in each of at least two nerves, or at least two of the following in one nerve, if all others are inexcitable and CMAP is >10 % of lower limit of normal (LLN): MNCV <90 % LLN (85 % if dCMAP <50 % LLN). DML >110 % of upper limit of normal (ULN) (>120 % if dCMAP <100 % LLN). pCMAP/dCMAP (ratio between CMAP obtained after proximal and distal stimulation) <0.5 and CMAP >20 % LLN. F-response latency >120 % ULN. Sensory conduction studies: sural SAPs are frequently normal in spite of reduced or absent SAPs in the upper limbs. Needle EMG is mostly complementary showing decreased motor unit recruitment; fibrillation potentials appear 2–4 weeks after onset if axonal degeneration occur.

AMSAN: none of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP <10 % LLN. SAPs < LLN.

AMAN: none of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP <10 % LLN. SAPs normal. dCMAP absent in all nerves or present in only one nerve with dCMAP <10%LLN.

Serial recordings are indicated for proper diagnosis and prognosis. In the very early course electroneurography (ENG) may be normal in up to 15 % of patients and may not distinguish different electrophysiological subtypes. In AIDP delayed DML, delayed or absent F waves and temporal dispersion may be more sensitive indicators than conduction slowing and CB in the intermediate nerve segments; the nadir of conduction slowing is 3–6 weeks after onset, corresponding to the clinical recovery stage and remyelination. AMAN may disclose transient conduction slowing and block within 3 weeks after onset and rapid normalization in parallel with clinical recovery; CMAP amplitudes have a rapid progressive decrement and gradually improve with clinically recovery without prolongation of DML, conduction slowing or excessive temporal dispersion. In acute motor-conduction-block neuropathy, an aborted form of AMAN, CBs rapidly resolve without excessive temporal dispersion or conduction slowing.

Other Laboratory Features

Antiganglioside antibodies are not specific or prognostic and not always suitable clinically. Ig anti-GM1 antibodies may be detected in the majority (64 %) of AMAN patients and in AMSAN as well as in AMSAN and acute motor-conduction-block neuropathy.

Liver function tests are often elevated.

35.2.1.6 Top Differential Diagnoses

Muscle: critical illness myopathy, polymyositis, rabdomyolysis, hypokalemia, hypophosphatemia.

Neuromuscular junction: myasthenia gravis (crisis), botulism, organophosphate poisonings, tick paralysis.

Polyneuropathies: AIP, critical illness polyneuropathy, vasculitis, diphtheria, heavy metals, or drug intoxications.

Polyradiculopathies: inflammatory or neoplastic meningoradiculopathies, CMV lumbosacral radiculomyelopathy.

Central Nervous System: West Nile and enterovirus poliomyelitis, transverse myelitis.

35.2.1.7 Therapy

Immunotherapy

In all patients, even if only mildly affected and able to walk with or without assistance, plasma exchange (PE) or IVIg (preferred in many centers because of greater convenience and availability) should be started early, preferably within the first 2 weeks. They are equally effective in improving the disability grade after 4 weeks as well as the duration of mechanical ventilation, mortality, and residual disability. PE: four to six alternate-day

exchanges (2–4 L each). IVIg: 2.0 g/kg body weight infused over 5 days.

In patients who continue to worsen, a repeated course of IVIg might be effective (not proven, trials and observational studies ongoing); combination of PE followed with IVIg is not superior compared to PE or IVIg alone. Combination of IVIg and intravenous methylprednisolone is no more effective than IVIg alone.

In patients who deteriorate after initial improvement (treatment-related clinical fluctuations in 5–10 % of cases), a second IVIg is given (2 g/kg in 2–5 days).

Three or more episodes of deterioration after 9 weeks from onset suggest Acute-onset CIDP (A.CIDP), which should be treated accordingly.

Indications for ICU Admission
Rapidly progressive severe weakness often with impaired respiration. Need for artificial ventilation (elective intubation if forced vital capacity less than 15 ml/kg or negative inspiratory force less than –20/–30 cm H_2O). Severe autonomic dysfunction (cardiac arrhythmias, marked fluctuations of blood pressure).

Supportive Care

35.2.1.8 Prognosis
Maximal weakness is reached within 4 weeks (at least 50 % of patients reach a nadir by 2 weeks). About 5 % of patients initially diagnosed with GBS have longer progression over 8 weeks (A-CIDP). Following the plateau phase, which lasts from several days to weeks, most patients recover a satisfactory function over several months, but only about 15 % of patients are asymptomatic 1–2 years after onset and 5–10 % remain persistently disabled or severely fatigued. GBS is potentially fatal: about 25 % of patients require artificial ventilation during a period of days to months, about 5 % die due to respiratory failure or distress syndrome, aspiration pneumonia, pulmonary embolism, cardiac arrhythmias, or sepsis related to acquired infections.

AIDP tend to have a longer progression and later nadir (18 vs 11.5 days), facial weakness (71 % vs 9 %), and more frequent need of artificial ventilation (27 % vs 9 %) in comparison to AMAN.

Risk Predictors for Artificial Ventilation The risk was found to be relatively lower (less than 2.5 %) in patients without CB of the common peroneal nerve and with a vital capacity of more than 81 % [12]. Days between onset of weakness and admission, Medical Research Council (MRC) sum score, and presence of facial and/or bulbar weakness were the main predictors of mechanical ventilation in the Erasmus GBS Respiratory Insufficiency Scale (EGRIS) [13].

Outcome Predictors The modified Erasmus GBS Outcome scale (mEGOS) takes into account the patient's age, presence or absence of preceding diarrhea, and disease severity; advanced age, preceding diarrhea, and low MRC sum score, calculated at admission and at 1 week, are independently associated with inability to walk at 1, 3, and 6 months [14].

35.2.2 Miller-Fisher Syndrome (MFS)

35.2.2.1 Definition
Acute syndrome of ataxia, ophthalmoplegia, areflexia with median peak at 1 week after onset.

35.2.2.2 Demographics
Incidence estimated at 0.09 per 100,000. More frequent in eastern Asia (20 % and 25 % of GBS in Taiwan and Japan) with male predominance (2 to 1) and mean age of onset in early forties. Onset is most common in spring. Most patients have an antecedent respiratory or gastrointestinal infection 1–3 weeks before onset (*C. jejuni* 20 %, *Haemophilus influenzae* 8 %). MFS is also anecdotally associated with autoimmune and neoplastic conditions.

35.2.2.3 Pathophysiology
Anti-GQ1b antibodies raised through molecular mimicry are detectable in most patients and may interact with GQ1b ganglioside concentrated in the oculomotor, trochlear, and abducens nerves

as well as in limb muscle spindles. Primary pathological changes of the uncomplicated form are unclear but early sensory nerve conduction studies are consistent with nerve demyelination or conduction failure along the axons rather than axonal loss. Sensory ataxia may be caused by selective involvement of muscle-spindle afferents.

35.2.2.4 Diagnosis

Clinical Features

Ophthalmoparesis may develop asymmetrically but becomes often complete; pupillary involvement is uncommon. Diplopia is the most frequent symptom at onset (39 %). Ataxia is evident in 21 % of patients at onset. Areflexia is detectable in 82 % of patients. Associated features may be facial diparesis (57 %), dysphagia (40 %), and dysarthria (13 %), distal paresthesias. Some patients may have MFS-AIDP overlap with limb weakness and respiratory involvement or incomplete forms with various combinations of ophthalmoplegia, facial or bulbar palsy, and sensory neuropathy. Overlap of MFS with Bickerstaff's brain-stem encephalitis (BBE) may have additional features of CNS involvement such as drowsiness and extensor plantar responses.

35.2.2.5 Top Differential Diagnosis

Other anti-GQ1b antibody syndromes: acute ophthalmoparesis, acute ataxic neuropathy, pharyngeal-cervical-brachial weakness, and BBE (ophthalmoplegia, ataxia, hypereflexia, and disturbed consciousness, associated to Ig anti-GQ1b antibodies in 66 % of cases). Brainstem stroke. Wernicke's encephalopathy, myasthenia gravis, botulism.

35.2.2.6 Diagnostic Markers

Blood IgG anti-GQ1b antibodies are detectable in up to 95 % of patients but are not specific or prognostic; they are not always suitable clinically.

CSF Most patients have elevated CSF proteins without significant pleocytosis; normal CSF proteins do not exclude the diagnosis.

MRI Imaging is unremarkable in most cases. Singleton cases may disclose brainstem abnormalities.

Neurophysiology SNAPs are initially reduced alone or out of proportion to prolongation of DML or slowing of sensory conduction velocities and return to normal with clinical improvement. CMAPs in arms and legs are usually normal. *Blink reflex* may be abnormal and reduced facial CMAP coincides with loss or mild delay of R1 and R2 responses. In some cases, abnormalities of visual, auditory, somatosensory, and motor-evoked potentials suggest a combined central and peripheral involvement. Anti-GQ1b antibody-positive MFS patients may have abnormal jitters that improve with clinical recovery and may have evidence of presynaptic neuromuscular transmission defect at high-frequency repetitive nerve stimulation up to 3 months after onset.

35.2.2.7 Therapy

There are no randomized, double-blind, placebo-controlled trials. Anecdotal patients are treated with IVIg or PE similarly to GBS.

35.2.2.8 Prognosis

Peak is at a median of 1 week. Median interval between onset and the beginning of recovery is 12–15 days. Recovery from ataxia and from ophthalmoplegia takes a median of 1 and 3 months. By 6 months, most patients are free from ataxia and ophthalmoparesis. The pure form is mostly self-limiting and benign. MFS-GBS or MFS-BBE overlap forms are described, particularly in children, and may require mechanical ventilation or lead to serious complications such as coma, ballism, cardiomyopathy from dysautonomia, lactic acidosis, and pain. Recurrences are rare but documented.

35.2.3 Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

35.2.3.1 Definition

Acquired demyelinating neuropathy of presumed autoimmune origin.

35.2.3.2 Demographics

Prevalence: from 1.97/100,000 (American Academy of Neurology – AAN research criteria) to 4.77/100,000 (European Federation of Neurological Societies and the Peripheral Nerve Society – EFNS/PNS diagnostic criteria). Incidence: 0.35/100,000 (AAN research criteria) – 0.70/100,000 (EFNS/PNS diagnostic criteria). Although all ages may be involved (including infancy), CIDP is most common after 40-years. Other possibly associated diseases: IgG or IgA MGUS (monoclonal gammopathy of undetermined significance), IgM MGUS without anti-MAG antibodies, HIV infection, various inflammatory or immunomediated systemic disorders. There are no clear-cut differences between idiopathic CIDP and CIDP associated with others disorders.

35.2.3.3 Pathophysiology

Both cellular and humoral immunity are implicated in the pathogenesis with variable mechanisms. No pathogenic antibody or definite triggering antigen have been identified. Demyelination is caused by macrophages recruited by activated T-cells and by complement-fixing immunoglobulins.

35.2.3.4 Clinical Features

Typical CIDP (80 % of cases) Symmetrical distal and proximal weakness, sensory loss and paresthesias, decreased or absent deep tendon reflexes; rare involvement of cranial nerves, respiratory insufficiency and dysautonomia. Disease course is steadily progressive or relapsing/remitting over at least 8 weeks. In the GBS-like presentation (A-CIDP) deterioration occurs for more than 8 weeks after onset or relapse at least three times; A-CIDP should be suspected with prominent sensory involvement at presentation.

Atypical CIDP *Asymmetric CIDP* or Lewis-Sumner syndrome or multifocal demyelinating neuropathy with persistent CBs: slowly progressive, asymmetric sensorimotor involvement in the distribution of two or more peripheral nerves, usually first in the upper, later in lower limbs and, rarely, cranial nerves.

Focal CIDP: localized to brachial or lumbosacral plexus or one or more peripheral nerves in an upper or lower limb.

Pure motor CIDP: selective involvement of motor fibers.

Pure sensory CIDP: gait ataxia and paresthesias (MNCV slowing and CBs may be present despite absence of motor symptoms).

Distal Acquired Demyelinating Symmetrical neuropathy (DADS): mainly sensory neuropathy associated in 2/3 of cases with anti-MAG antibodies (see paraproteinemic neuropathies); cases without anti-MAG antibodies respond to immunotherapy similarly to typical CIDP.

Other features: subclinical signs of CNS involvement may occur in up to 50 % of cases (prolonged central motor conduction times, periventricular white matter MRI hyperintensities). Multiple Sclerosis-like syndrome may rarely occur.

35.2.3.5 Diagnostic Markers

CSF Increased CSF protein content with blood cell count less than 10/mm^3 occurs in approximately 90–95 %.

Imaging MRI discloses gadolinium enhancement and/or hypertrophy of the cauda equina and lumbosacral nerve roots, and of brachial and

lumbosacral plexuses; STIR images are more sensitive (66.7 %) than T1-weighted images or gadolinium enhancement. US may reveal normal, mildly, or regionally enlarged nerves.

Neurophysiology Sensitivity for motor nerves may be improved by exhaustive studies of the four limbs including proximal stimulation in the upper limbs; somatosensory-evoked potentials may be useful to demonstrate abnormal proximal sensory conduction.

The EFNS/PNS diagnostic criteria have 81.3 % sensitivity and 96.2 % specificity [15].

Definite CIDP Criteria for definite CIDP include at least one of the following in two nerves: at least 30 % reduction of MNCV; at least 50 % prolongation of DML; at least 30 % prolongation of F-wave latency; CB with at least 50 % reduction of the proximal negative peak CMAP relative to distal; abnormal temporal dispersion (at least 30 % increase between the proximal and distal negative peak CMAP); prolongation of distal CMAP duration (median nerve 6.6 ms, ulnar 6.7 ms, peroneal 7.6 ms, tibial 8.8 ms).

Probable CIDP At least 30 % amplitude reduction of the proximal negative peak CMAP relative to distal.

Possible CIDP One the abovementioned findings is detectable in only one nerve.

In probable and possible CIDP, supportive criteria may come from other laboratory tests and from objective clinical improvement after immunotherapy [16].

Nerve biopsy Sural or superficial peroneal nerves are analyzed, if affected. Positive findings are not specific and negative findings (normal nerve or chronic axonal degeneration) do not exclude the diagnosis. Supportive features include: hypertrophic de-remyelination with onion-bulb formations (possible overlap with CMT1), variations between fascicles, endoneurial edema, and endoneurial mononuclear infiltration.

35.2.3.6 Therapy

Patients with very mild symptoms who are not functionally impaired may be monitored without treatment. Up to 80 % of patients with adulthood or childhood typical CIDP respond to one of the three first-line therapies: IVIg, corticosteroids or PE; whether a combination of IVIg and steroids may offer additional benefit and greater chance of remission remains to be proven. IVIg should be the first choice for motor CIDP; if steroids are used, patients should be monitored closely for deterioration. As a general rule, if the first-line treatment is effective, continuation should be considered until the maximum benefit is achieved and then the dose reduced to find the lowest effective maintenance dose. IVIg is most often used because of its safer profile and better short-term efficacy.

IVIg may represent an ideal first-line choice in severely disabled patients who need rapid improvement provided that there are no absolute (IgA deficiency) or relative (renal failure, hyperviscosity syndrome) contraindications [17]. A first course is done by giving 2 g/kg intravenously in 5 days. Long-term management is empiric: IVIg can be maintained in doses over 1 g/kg over 1–2 days every 3 weeks but the appropriate dose and/or frequency is individualized (0.4–1.2 g/kg every 2–6 weeks). Once recovery is complete or stable (usually within 2–4 months) the therapy should be tapered and eventually discontinued as patients may have a monophasic course without relapse for months or years.

Corticosteroids represent an ideal first-line choice in patients with milder disease and without contraindications due to the higher likelihood of long-term remission. In long-term maintenance therapy, patients should be monitored for steroid-related side effects and complications. There is no consensus about whether to use oral daily or alternate-day regimens or intermittent pulsed intravenous or oral regimens. Prednisone 1–1.5 mg/kg is given daily as a single oral dose; once improvement begins, usually within 2–4 weeks, tapering the daily to alternate-day treatment (1–1.5 mg/kg every other day until complete or stable recovery) will lessen potential side-effects; further tapering, usually after

6 months, may be done by decreasing the dose by 5 mg every 2–3 weeks. Pulsed oral dexamethasone is given at a dosage of 40 mg daily for 4 days repeated at 4 weekly intervals for 6 months and then tapered over another 6 months [18]. Intermittent intravenous methylprednisolone is used at a dosage of 1000 mg daily for 3–5 days and then 1000 mg monthly.

Plasma-exchange (*PE*). Because the response is transient and CIDP may worsen after stopping it, PE needs to be combined with other treatments for stabilization or may be considered as a second-line temporary measure in the treatment of IVIg and steroid-unresponsive CIDP. A regimen of five to six exchanges over 2 weeks (total exchanged plasma 200–250 mL/kg) may be beneficial over the short term (1–2 months) in inducing a rapid remission in patients without contraindications.

If the response of the first-line treatment is inadequate or the maintenance doses of the initial treatment result in adverse effects, therapy should be shifted to another first-line treatment. Second or third-line immunosuppressive therapies should be reserved for severely affected patients refractory to any of the first-line treatments; the efficacy of these therapies has yet to be proven.

35.2.3.7 Prognosis

Onset is progressive (symptoms develop for more than 8 weeks) in the majority of patients (~80 %), acute (symptoms develop within less than 4 weeks), or subacute (symptoms develop within 4–8 weeks). The course is relapsing-remitting ("two episodes with remission and relapse unrelated to therapeutical changes") in ~ 15 % of patients and progressive in the remaining cases [19].

Progressive course, CNS involvement, pathologically active demyelination, and severe axonal loss are associated with poorer long-term prognosis and disability [20]. Significant disability may result also from symptoms such as fatigue (severe in up to three quarters of patients), pain (up to one third), and refractory tremor (more than half of patients). Mild autonomic genitourinary or gastrointestinal symptoms are relatively common, but severe autonomic dysfunction should raise doubts about the diagnosis of CIDP.

In a recent retrospective series, approximately 40 % of patients had no or non-disabling symptoms, 75 % were able to work and walk, and 24 % had a severe handicap (Rankin score >2). Long-term mortality due to neurological deficits (bulbar involvement and respiratory failure) ranged from 1.3 to 9 %. Ventilatory involvement was relatively rare, but abnormal phrenic nerve conductions were evident in the majority of patients [21]. A-CIDP may have had a higher risk of ventilatory failure with a mortality rate similar to GBS.

Around 80 % of patients are responders to therapies but 40 % of treated patients remain treatment-dependent in the long term [19]; 1 year after initiating IVIg, up to 60 % patients need regular courses of therapy. Treatment-dependence may be associated with IVIg responsiveness and corticosteroids resistance, longer delay from onset to effective therapy, and with multifocal clinical presentation; steroids might be associated with more frequent treatment withdrawal [17, 22]. IVIg is less often discontinued due to inefficacy, adverse events, or intolerance when compared with IV methylprednisolone.

Patients responding to IV methylprednisolone have fewer relapses after discontinuation of treatment compared to responders to IVIg. By evaluating the CDAS (CIDP Disease Activity Status) score in more than 100 patients, the long-term (mean duration = 6.4 years) outcome was as follows: 11 % of patients were "cured" (off treatment for ≥5 years with a stable examination), 20 % "in remission" (stable and off treatment with a follow up <5 years), 44 % had a "stable active disease" (requiring ongoing therapy for at least 1 year), 7 % had an improvement after recent initiation of therapy (for at least 3 months but less than 1 year), 18 % had an unstable active disease (treatment naïve or treatment refractory) [23].

CDAS may be a useful tool in order to identify patients with long-term inactive disease off therapy (CDAS 1 and 2) and those who are treatment refractory (CDAS 5B and CDAS 5C) as well as to avoid overtreatments.

CIDP variants may have different courses and sometimes response to treatment compared to typical CIDP.

Pure sensory CIDP (up to 35 % of CIDP cases, the most frequent atypical CIDP), which includes CISP (chronic inflammatory sensory polyradiculoneuropathy with predominant sensory ataxia in lower limbs) may be either progressive or monophasic and respond either to IVIg or corticosteroids. *Pure-motor CIDP* (~10 % of CIDP cases) has a good response to IVIg and may deteriorate after corticosteroid treatment.

Asymmetric CIDP (15 % of CIDP cases) has frequent involvement of cranial nerves (25 % of cases) and progressive course (~ three quarters of cases). Despite treatment (corticosteroids and IVIg seem to be equally effective), the course is more often slowly progressive.

Focal CIDP has a slowly progressive course over one to several years, without progression to other limbs and is equally responsive to IVIg or corticosteroids.

A relatively small subgroup of treatment-resistant patients mostly affected by a rapidly progressive course with predominantly motor involvement and/or disabling tremor, were associated recently with immunoglobulin G4 (IgG4) immune reactivity and serum Ab against neurofascin 155, contactin1 (CNTN1) and contactin1-associated protein-1 (CASPR1) which bind paranodes and are detectable by immunocytochemistry and ELISA. Rituximab was an effective rescue therapy in those patients [24].

In childhood, the majority of patients (60 %) have a chronic onset and a relapsing course (70 %), and respond similarly (approximately 80 %) to corticosteroids or IVIg (most frequently used first-line monotherapy). Childhood CIDP usually has a favorable course [25].

35.2.4 Multifocal Motor Neuropathy (MMN)

35.2.4.1 Definition

A treatable immune-mediated peripheral neuropathy which frequently mimics a motor neuron disease, characterized by slowly progressive asymmetric distal weakness without significant sensory loss, persistent motor CB, evidence of IgM anti-GM1 in about 50 % of cases, and response to IVIG in up to 90 % of patients.

35.2.4.2 Demographics

Prevalence: 1–2 per 100,000 with male-to-female ratio of approximately 2.6:1. Median age of onset: around 40 years with the majority of cases presenting between 20 and 50 years. Children may be exceptionally affected. In some cases, MMN co-occurs with celiac disease and Hashimoto's thyroid disease. First-degree family members also have higher incidence of type 1 diabetes, celiac disease and Hashimoto's thyroid disease.

35.2.4.3 Pathophysiology

A nodo-paranodopathy likely caused by an immune attack against the node of Ranvier (e.g., IgM to GM1) with formation of membrane attack complexes, which disrupts and displaces ion channels and paranodal structures, and compromises nerve conduction, resulting finally into axonal degeneration [26].

35.2.4.4 Diagnosis

Current criteria rely upon clinical and electrophysiological features reviewed by the Task Force of EFNS/PNS; the diagnosis may be supported by laboratory and imaging data [27].

35.2.4.5 Clinical Features

Slow or stepwise progressive weakness developing over months or years with a multifocal asymmetric distribution in individual nerves, usually starting and remaining prominent in the distal arms. Cramps and fasciculations are frequent in the affected motor nerves with no or slight amyotrophy in the early stages, reflecting the clinical expression of CB. Decreased muscle bulk may develop over time due to secondary axonal degeneration. Weakness is often exacerbated by cold. Predominant lower limb involvement at onset accounts for only 10 % of cases. Deep tendon reflexes are usually depressed or absent in affected territories but may be normal or even brisk in rare cases. Sensory examination should be normal except for minor vibration sense abnormalities in the lower limbs. In some cases, MMN may have a progressive stepwise course; a few cases may have an AIDP-mimicking acute onset but further course and response to treatment are typical of classical MMN.

35.2.4.6 Laboratory Features

Immunology The most typical finding, detected in 40–50 % of cases, is significant titers of serum IgM autoantibodies binding to ganglioside GM1 and, less frequently, to other glycolipids including asialo-GM1, GD1A, or GM2. Serum IgM against NS6S heparin disaccharide have the same positivity as that of anti-GM1 antibodies, suggesting that concomitant tests for both antibodies would increase the seropositivity to 64 %, but anti-NS6S antibodies may be detected also in sensory neuropathies [28]. The accuracy of antibodies has limitations and their absence does not exclude the diagnosis.

CSF Normal or <1 g/L protein content is a supportive criteria for diagnosis.

MRI Although non-specific, MRI of the brachial plexus may be a supportive criterion showing increased signal intensity on T2-weighted scans or contrast-enhancement on T1 sequences.

Electrophysiology CB in motor nerve fibers outside the usual sites of entrapment/compression with normal SNCV in the same limb segments are the disease hallmark. Criteria for definite and probable CB have been revised by EFNS/PNS [27]. Some patients with typical MMN have no detectable CB probably because CBs are activity dependent or located in segments not assessed by the routine electrophysiological tests. More sensitive techniques such as transcranial magnetic stimulation, triple stimulation, and transcutaneous cervical root stimulation may be useful to detect CB located in the proximal segments of motor nerves. EMG reveals reduced recruitment in weak muscles and, once secondary axonal loss has established, positive sharp waves and fibrillation potentials.

Other Laboratory Features may be helpful to discover or rule out concomitant diseases or alternative causative disorders.

35.2.4.7 Top Differential Diagnosis

Motor neuron disorders. CIDP. Myopathies. Disorders of nerve roots and plexus.

35.2.4.8 Therapy

IVIg are the first-line treatment and are effective in 79–86 % of patients resulting in an improvement of muscle strength, sometimes accompanied by disappearance of partial CB but without correlations with anti-GM1 positive patients.

IVIg are given at the initial dose of 2 g/kg given in 5 consecutive days; most responders require long-term maintenance with varying intervals and doses. A single course is not sufficient to establish responsiveness to IVIg.

In patients who do not respond to IVIg, in patients with a declining response to IVIg, in patients in whom IVIg are contraindicated, alternative therapies are available. IV cyclophosphamide was reported to be effective in more than 70 % of patients; experts do not recommend it because of short- and long-term toxicity and lack of clear evidence of efficacy. Rituximab can be administered at a dose of 375 mg/m^2 every week to achieve peripheral B cell depletion.

35.2.4.9 Prognosis

The extent of axonal degeneration may be a valuable prognostic factor regarding clinical course and response to treatment. An elevated titer of anti-GM1 antibodies and definite CB may be associated with IVIg responsiveness. Some rare patients achieve spontaneous remission but more than two-thirds of patients are IVIg-dependent.

Long-term efficacy of IVIg has been addressed by numerous retrospective studies of patients who were under treatment for several years. After years the effectiveness of IVIg often declines due to axonal degeneration [29]. When given at high doses every month, IVIg improve muscle strength and functional disability, decrease the number of CB and the extent of axonal degeneration [30]. Early initiation of IVIg followed by a maintenance treatment is the only intervention that may prevent axonal loss and a more severe outcome; IVIg non-responders have often a longer duration of disease before the first treatment [31].

35.2.5 Paraproteinemic Neuropathies

Key Facts

- **Terminology and definitions** – Clinically and pathogenetically heterogeneous neuropathies sharing the presence of an abnormal spike of β-γ serum proteins.
- **Clinical features** –
  MGUS prevalence: 3.2 % in the population above 50 years and 7.5 % above 80 years. CIDP may be related to MGUS in 15 % of cases.
  POEMS: severe predominantly motor and sensory polyneuropathy most frequently associated with IgG or IgA monoclonal proteins bearing λ light chains.
  Anti-MAG IgM-Ab: prevalence of 20–40/100,000 in older than 50 years. Anti-Mag is a chronic slowly progressive, mainly sensory and distal demyelinating neuropathy with tremor (sometimes disabling).
- **Diagnostic markers**
  - **Blood**
    POEMS: IgG or IgA monoclonal proteins bearing λ light chains.
    Anti-MAG neuropathy: IgM antibodies against the MAG glycoprotein.
  - **CSF** – *POEMS* increased CSF proteins.
  - **Imaging** – *POEMS*: osteosclerotic bone lesions.
  - **Neurophysiology** – *Anti-MAG* shows reduced CV with disproportional delay of DML.
    POEMS – has diffuse demyelinating neuropathy with early decrease of CMAP.
- **Top differential diagnoses** – Hereditary and inflammatory demyelinating neuropathies.
- **Prognosis**
  - **Principles of treatment**
    Anti-MAG: no evidence of efficacy and safety of any long-term therapy.
    POEMS – Rx-therapy in the presence of sclerotic plasmacytoma. Alkylating-agents. Steroids.
  - **Disability**
    Anti-MAG: most patients have a favorable functional prognosis with only 25 % of patients becoming disabled after 10 years and 50 % after 15–20 years.
    POEMS: is chronic and invalidating; 50 % of patients are bedridden; mean survival ranges from 12–33 to 165 months. VEGF correlate with the activity of disease and response to therapy.

35.2.5.1 Definition

Paraproteinemic neuropathies are a clinically and pathogenetically heterogeneous group of neuropathies sharing the presence of an abnormal spike in the β-γ region of serum protein electrophoresis and/or by serum immunofixation. The monoclonal gammopathy may indicate an underlying clonal B-cell expansion, which may appear in the context of an hematological malignancy [multiple myeloma; heavy chain disease; primary amyloidosis (amyloidosis light-chain – AL); Waldenström macroglobulinemia (WM), B cell lymphoma or chronic lymphocytic leukemia] or, in more than two thirds of patients, may be not associated with a lymphoproliferative disorder [monoclonal gammopathy of undetermined significance (MGUS)]. MGUS may evolve into a malignant form after several years (around 1 %/year of MGUS cases may progress to malignancy).

35.2.5.2 Demographics

MGUS occurs in 3.2 % in the population above 50 years and in 7.5 % of those above 80 years. In those individuals the neuropathy is often the only clinical manifestation and may be symptomatic in up to 35 % of cases; the prevalence of neuropathy is higher in patients with IgM than with IgG or IgA MGUS. In hematological malignancies, neuropathy may occur in up 50 % of patients with WM (in which it may be the only manifestation of the disease in up to one third of cases), 15 % of those with multiple myeloma, 20 % with AL, 8 % with lymphoma [32].

35.2.5.3 Pathophysiology

The mechanisms are heterogeneous and may be related to infiltration of neoplastic cells, specific immunoreactivities of the circulating paraproteins, hyperviscosity, cryoglobulinemia, or

upregulation of proinflammatory cytokines and growth factors.

35.2.5.4 Clinical Features

Heterogeneous presentations correlate with different disease mechanisms. Major syndromes are recognizable.

The most frequent presentation is related to IgM antibodies reacting against Myelin Associated Glycoprotein (MAG) with a highly stereotyped clinical picture of a chronic slowly progressive, mainly sensory, demyelinating neuropathy.

CIDP may be related to IgG or IgA immunoglobulins (monoclonal gammopathy can be detected in up 15 % of CIDP cases).

A rare syndrome of chronic sensory ataxic neuropathy, ophthalmoplegia and bulbar dysfunction may be also related to IgM MGUS with antibodies against disialosyl group shared by several gangliosides (CANOMAD: chronic ataxia neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, disialosyl antibodies).

A progressive motor-sensory and autonomic neuropathy with early involvement of small fibers (painful dysesthesias, diminished pain, and temperature sensation) is associated with AL amyloidosis or amyloidosis occurring in the setting of WM, multiple myeloma, or other lymphoproliferative disorders.

35.2.6 POEMS

POEMS [*P*eripheral neuropathy, *O*rganomegaly, *E*ndocrinopathy, *M*onoclonal gammopathy, and *S*kin changes (rusty hyperpigmentation, white nails, hypertrichosis)] is a severe, subacute, predominantly motor neuropathy. Demyelinating polyradiculoneuropathy, sclerotic bone lesions, elevated vascular endothelial growth factor (VEGF), and the occurrence of Castleman disease are the major criteria for the diagnosis.

POEMS manifests as a neuropathy with early decrease of CMAP and increased CSF proteins, possibly related to the upregulation of proinflammatory cytokines (markedly increased levels of VEGF correlate with the activity of disease and response to therapy). Pulmonary hypertension, renal failure, thrombotic events, and congestive heart failure may be also syndromic features.

35.2.6.1 Therapy

Rx-therapy is first line in the presence of sclerotic plasmacytoma. Corticosteroids may be useful, but alkylating agents are the basis of medical treatment.

35.2.6.2 Prognosis

POEMS is a chronic and invalidating disease and many patients (50 %) are bedridden due to the neuropathy. In available studies the mean survival ranged from 12 to 33 months [33] to 165 months in a more recent series [34]. Nail clubbing and extravascular fluid overload were associated with shorter survival. Management depends on treatment of the underlying plasma cell dyscrasia and may include radiation therapy, chemotherapy and/or hemopoietic cell transplantation. VEGF level correlates with the activity of the disease.

35.2.7 Neuropathy with Anti-MAG IgM

35.2.7.1 Definition

Demyelinating neuropathy associated with IgM antibodies against the MAG glycoprotein mostly concentrated in uncompact myelin.

35.2.7.2 Demographics

Prevalence in the population above 50 years may be at least 20–40 per 100,000. Almost 80 % of patients with anti-MAG IgM have IgM MGUS while most remaining patients have WM which is frequently indolent.

35.2.7.3 Pathogenesis

Complement mediated demyelination triggered by anti-MAG IgM M-proteins

35.2.7.4 Clinical Features

Chronic, slowly progressive, symmetric, distal predominantly sensory demyelinating neuropathy with paresthesias, hypo-dysesthesia, cramps of the lower limbs, unsteadiness of gait, often associated with intentional and postural tremor in the upper limbs. Examination discloses signs of large-fiber involvement with ataxia, decreased distal vibration sense, Romberg's sign, with minor distal motor deficit. Tremor may be the presenting symptom and may be disabling. Onset is most frequently in the sixth-seventh decade.

35.2.7.5 Diagnostic Markers

Blood Sera anti-MAG IgM are detectable by commercially available ELISA systems or by cumbersome western blot assays against home-made isolated myelin. Indirect immunofluorescence may detect deposition of IgM, IgG, IgA heavy and light chains in control bioptic nerves thus suggesting an immunomediated attack event in patients with uncharacterized reactivity to nerve [35]. A careful survey should be done to rule out hematological malignancies.

CSF CSF analysis is unnecessary in typical cases. In almost all patients it discloses increased proteins in a CIDP-overlapping range of 80–100 mg/dl. Cytofluorimetry may investigate malignant cells in atypical cases.

Neurophysiology Reduced SNCV and MNCV with disproportional delay of DML. CBs are rare and should raise the suspicion of CIDP. Relevant reduction of NCV (slowing of MNCV, often in the range of 15–25 m/s) diverges from mild clinical impairment.

Nerve biopsy is unnecessary in typical cases. It discloses a demyelinating neuropathy with typical ultrastructural widening of outer myelin lamellae in 90 % of cases; direct immunofluorescence discloses deposits of IgM at the periphery of residual myelinated fibers.

35.2.7.6 Therapy

Patients unimpaired in their daily life: symptomatic therapy for tremor and paresthesias, neurological and hematological follow-up. Some patients with significant functional impairment may benefit from rituximab (4 weekly infusions of 375 mg/m^2), but placebo control trials failed to provide any clear evidence of efficacy, even for a 1-year follow-up [36] and indications to treatment should consider potential side-effects including progressive multifocal leukoencephalopathy (PML). Evidence of long-term term efficacy and safety are lacking also for other immune therapies.

35.2.7.7 Prognosis

Anti-MAG neuropathy is a prognostically favorable disease: patients with neuropathy, IgM paraprotein, and anti-MAG have a lower risk of evolution into malignancy than patients without neuropathy or without anti-MAG reactivity. The neuropathy is slowly progressive and most patients have a long-term favorable functional prognosis with only 25 % of patients becoming disabled after 10 years and 50 % after 15–20 years. A minority of patients have a CIDP-like faster progression with severe ataxia or motor involvement.

35.2.8 Non-systemic Vasculitic Neuropathy (NSVN)

Key Facts

- **Terminology and definitions** – Vasculitides are due to secondary ischemic injury of peripheral nerves caused by inflammatory infiltration and destruction of the afferent vessel walls.
- **Clinical features**
- PNS vasculitides annual incidence is 0.6–1.2/100,000; incidence of NSVN is 5/million. Vasculitic neuropathies cause subacute or slowly progressive, sometimes stepwise, multifocal, asymmetric peripheral neurological deficits. They may appear as painful multiple mononeuropathy (45 % of cases), asymmetrical polyneuropathy (30 %), and distal symmetrical polyneuropathy (25 %).
- **Diagnostic markers**
  - **Blood** to assess non-neurological organ dysfunction.
  - **CSF** may demonstrate pleocytosis (5 %), elevated CSF proteins (30 %), and oligoclonal bands in NSVN.
  - **Nerve biopsy** – '*Definite*' vasculitic neuropathy shows inflammation within the vessel wall and vascular damage in the epineurium. Perivascular inflammation and signs of chronic vascular injury identify definite but inactive vasculitis.
  - **Neurophysiology** consistent with a primary axonal, sensory-motor process; "pseudo-CB" occur in 10–25 %.
- **Top differential diagnoses** – CIDP variants, HNPP, amyloidosis, lymphomatosis; different forms of vasculitides (Churg-Strauss, PAN, etc.)
- **Prognosis**
  - **Principles of treatment** – First-line therapy: steroids alone or associated with cyclophosphamide.
  - **Disability** usually not fatal, NSVN may become systemic in 10 % of patients. Most patients remain independent in daily activities; 60 % have chronic pain. Mortality rates: 4–15 % in NSVN (21–31 % in SVN); 5-year survival: 85 % (75 % in SVN). Relapse rate: 32 % in NSVN.

35.2.8.1 Definition

"Vasculitides" are characterized histologically by an inflammatory infiltration and destruction of the vessel walls with secondary ischemic injury to the involved tissues.

Peripheral nerve vasculitis may occur in up to 60–70 % of patients with systemic vasculitides which may manifest either as primary diseases or as secondary disorders related to various diseases ranging from rheumatological conditions to infections, malignancies, or inflammatory bowel diseases [37]. Peripheral nerve vasculitides may also occur as non-systemic or localized vasculitides, which are restricted to PNS over a prolonged follow-up. Localized vasculitides encompass: non-systemic vasculitic neuropathy (NSVN) which includes non-diabetic radiculoplexopathy and some cases of Wartenberg's migrant sensory neuritis; diabetic radiculoplexus-mononeuropathies; localized cutaneous vasculitides such as the cutaneous form of polyarteritis nodosa (cPAN).

35.2.8.2 Demographics

Incidence and prevalence are not estimated. It was claimed that PNS vasculitides have an annual incidence of 0.6–1.2 per 100,000 and NSVN of five cases per million. In certain series, NSVN was the most frequent PNS vasculitis, equivalent to PAN and microscopic polyangiitis [38]. Onset is around 60 years and women seem to be preferentially affected.

35.2.8.3 Pathophysiology

NSVN is mainly a microvasculitis of the smallest arterioles (< 40 μm), endoneurial microvessels (capillaries), and venules. Occasionally NSVN affect large arterioles and small arteries. Vasculitis is an axonopathy affecting mixed (sensory-motor) and purely sensory cutaneous nerves.

Pathogenesis implies a cell-mediated autoimmune disorder.

35.2.8.4 Clinical Features

Presentation is similar to systemic vasculitic neuropathies (SVN) developing subacute or slowly progressive, sometimes stepwise, multifocal asymmetric neurological deficits. Reported presentations include: 45 % multiple mononeuropathy, 30 % asymmetrical polyneuropathy (overlapping multifocal neuropathy), and 25 % distal symmetrical polyneuropathy. Both motor and sensory nerves are affected but 15 % of cases have predominantly sensory findings. Pain occurs in up to 80–96 % of patients. Systemic symptoms are uncommon and mild but 30 % of patients have weight loss and 10–15 % suffer fever. Affected nerves derive frequently from the lumbosacral plexus (common peroneal nerve or peroneal division of the sciatic); in the upper limbs the ulnar nerve is more commonly affected than median, radial and more proximal nerves.

Among clinical variants, cPAN affects the small-to-medium-sized arteries in the deep dermis and panniculus resulting in characteristic, painful, recurrent, often ulcerated nodes in the skin of the lower limbs; skin manifestations include also livedo racemosa, gangrene, urticaria, and bullae. Multifocal neuropathies in the lower limbs follow closely the distribution of the skin lesions. Other variants are represented by diabetic lumbosacral radiculoplexopathy (LSRP) and the analogous "non-diabetic LSRP" which is distinguished by its progressive evolution from the rare acute, painful, idiopathic, monophasic lumbosacral plexopathy syndrome (a regional variant of brachial neuralgic amyotrophy).

35.2.8.5 Diagnosis

The interval between onset and diagnosis is usually longer in NSVN (6 months) than in SVN. Painful, stepwise progressive, distal predominant, asymmetrical multifocal neuropathies suggest vasculitis, even if the clinical course is of several years.

Electrodiagnostic studies should be extensive in order to assess for asymmetries and non-length-dependent signs. Neurophysiology is consistent with a primary axonal, sensory-motor process; "pseudo-CBs" occur in 10–25 % of cases reflecting axonal degeneration; persistent, ischemia-induced, demyelinating partial motor CBs are rare.

Laboratory tests are done to assess non-neurological organ dysfunction, measure systemic inflammation, and investigate specific causes of multifocal neuropathy or vasculitis.

CSF Lumbar puncture should be considered in patients with proximal involvement to rule out malignancies or meningeal infections; in NSVN it may demonstrate pleocytosis (5 %), elevated CSF proteins (30 %), and oligoclonal bands.

Nerve or nerve/muscle biopsy is mandatory. The sural nerve or the superficial peroneal nerve plus the peroneus brevis muscle are biopsied most commonly, provided that they are clinically and neurophysiologically affected. Pathological criteria for active *definite vasculitic neuropathy* are as follows [39]: evidence of inflammation within the vessel wall and signs of vascular damage (fibrinoid necrosis, endothelial loss/disruption, loss/fragmentation of internal elastic lamina, acute thrombosis, hemorrhage), usually in the epineurium. Perivascular inflammation and signs of chronic vascular injury identifies definite but inactive vasculitis. Sensitivity of a definite nerve biopsy is 50–60 %; yield of muscle biopsies are similar. Pathological criteria for *probable vasculitic neuropathy* are not uniform [39].

35.2.8.6 Top Differential Diagnoses

Prior to biopsy: other causes of asymmetrical/multifocal neuropathy (e.g., CIDP variants, HNPP, amyloidosis, lymphomatosis).

Pathologically definite/probable vasculitis: primary (e.g., Churg-Strauss syndrome, essential mixed non-HCV cryoglobulinemia, PAN) or secondary (connective tissue disease, e.g., rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome; infection-related vasculitis, e.g., HBV, HCV, HIV, CMV, leprosy, Lyme disease; malignancy-related vasculitis).

35.2.8.7 Therapy and Prognosis

Natural history of untreated NSVN is unknown, but approximately 10 % of cases may evolve into systemic vasculitis.

Therapy is mandatory with the exception of improving and stable patients without recent pathological evidence of active vasculitis. Clinical trials are lacking [39]. First-line immunosuppressive therapies: oral prednisone 1 mg/kg/day or pulse IV methylprednisolone in severe, rapidly progressive NSVN. Combination therapy with IV cyclophosphamide, methotrexate, or azathioprine is advised in rapidly progressive NSVN and patients non-responders to monotherapy. Maintenance therapy by low-dose prednisone (5–7.5 mg daily) or azathioprine (1–2 mg/kg/day) or methotrexate (20–25 mg/week) for 18–24 months is advisable; probable remission is considered in the absence of clinical worsening after a 6-month follow-up.

At presentation most patients are still independent in activities of daily living. Approximately 50 % can walk without assistance, 35 % require walking aids, 15 % are non-ambulatory. NVSVN is usually not fatal: Most patients remain independent in daily activities and ambulation, although up to 60 % have chronic pain. Mortality rates of NSVN range from 4 to 15 % (21–31 % in SVN); 5-year survival is approximately 85 % (75 % in SVN). Relapse rate is approximately 32 % in NSVN; relapses (median interval = 15 months after onset of treatment) may occur either after discontinued therapy and in maintenance therapy.

35.2.9 Diabetic Neuropathies

Key Facts

- **Terminology and definitions** – Neuropathies associated with diabetes DM or prediabetes.
- **Clinical features** – Ten percent present with neuropathy at initial diagnosis of DM and 50 % after 20 years.
- **Diagnostic markers** – Diabetic neuropathies may occur as: 1 – Symmetrical neuropathies (DSP; SFN; autonomic neuropathy); 2 – Radiculoplexopathy; 3 – Cranial neuropathies; 4 – Limb mononeuropathy; 5 – Truncal radiculopathy.
  - **Blood** – Uncontrolled, or long lasting hyperglycemia.
  - **Neurophysiology** – Routine electrodiagnostic tests may be normal in SFN and in autonomic neuropathy.
  - **Autonomic tests** – Sympathetic skin reflex, quantitative sensory testing (QST), beat-to-beat HRV.
  - **Skin biopsy** – Can demonstrate the reduction of intraepidermal nerve fiber density in affected regions in *SFN*, and in *autonomic neuropathies.*
- **Top differential diagnoses** – Mono-plexo and polyneuropathies of different origin.
  Autonomic Neuropathy: Hereditary amyloidosis; Idiopathic immune-mediated and Paraneoplastic autonomic neuropathy.
- **Prognosis**
  - **Principles of treatment** – Prevention and treatment require an optimum glycemic control. Supportive and symptomatic medical measures.
  - **Disability**
    DSP is slowly progressive; can stabilize or improve with tight control of diabetes.
    Autonomic neuropathy increases the risk of adverse cardiovascular events. *LSRP* has a monophasic, self-limiting evolution.

35.2.9.1 Definition

Neuropathies associated with diabetes mellitus (DM) or prediabetes (impaired fasting glucose or impaired glucose tolerance) after the exclusion of other causes.

35.2.9.2 Demographics

Approximately two-thirds of patients with type 1 DM (T1DM) and with type 2 DM (T2DM) diabetes have symptoms and/or signs of neuropathy. The percent of patients with neuropathy is up to 10 % at the time of initial diagnosis of DM and up to 50 % after 20 years. The prevalence of neuropathy increases with poor glycemic control and age. Half of diabetics have a distal symmetric polyneuropathy (DSP), a quarter have carpal tunnel syndrome (CTS), 5 % have an autonomic neuropathy, and 1 % have an asymmetrical proximal neuropathy. Neuropathic pain occurs in about 10–20 % of the diabetic population, and in about 40–60 % of patients with documented neuropathy [40].

35.2.9.3 Clinical Features and Terminology

Symmetrical Neuropathies DSP; small-fiber-neuropathy (SFN); autonomic neuropathy. Episodic symmetrical neuropathies: treatment-induced neuropathy; diabetic neuropathic cachexia (DNC). Asymmetrical/focal and multifocal neuropathies; lumbosacral radiculoplexopathy (LSRP alias Bruns–Garland syndrome; diabetic amyotrophy); truncal radiculopathy; cranial neuropathies; limb mononeuropathies; multiple mononeuropathies.

Distal Symmetric Polyneuropathy (DSP) represents a continuous clinical spectrum influenced by the prevalent or mixed involvement of large or small fibers. It may be silent or manifest, usually with decreased feeling or tingling in toes, and evolves according to a stock-and-glove pattern with burning dysesthesias, allodynia, hyperalgesia, and electrical or shooting neuropathic pain. Thermal sensibility can be reduced in isolation or combination with diminished muscle stretch reflexes, light touch sensation, sensibility to pressure and vibration, and decreased joint position sense with postural instability and, rarely, ataxia. Distal weakness and wasting are a late event.

Small Fiber Neuropathy (SFN) manifests with spontaneous pain of a deep, burning, stinging, aching type, and allodynia to light touch. It is often accompanied by autonomic neuropathy.

Autonomic Neuropathy ranges from subclinical functional impairment of cardiovascular reflexes and sudorimotor function to severe cardiovascular, gastrointestinal, and genitor-urinary dysfunctions (see Chap. 36).

Radiculoplexopathy (LSRP) affects the lumbosacral or, rarely, the cervical plexus. LSRP is unrelated to the duration of disease; most patients are middle or old aged and have mild T2DM and concomitant weight loss. Onset is acute or subacute with burning or lancinating pain in the anterior thigh followed by days or weeks of difficulty in walking and climbing stairs with wasting and weakness of the quadriceps, iliopsoas, gluteus and, to a lesser extent, hamstring and anterior tibialis muscles; knee and ankle jerks are usually lost. The opposite leg may become affected is some cases after days or months. Progression may be steady or stepwise and may continue for many months before the disease stabilizes. Up to 60 % of cases overlap with DSP, disclosing a more gradual onset.

Cranial Neuropathies Unilateral palsies of the third and sixth cranial nerves often heralded by transient frontal pain, with acute onset and progression over 1–2 days. Third nerve palsy is usually nearly or fully complete but spares the pupillary reflex.

Limb Mononeuropathy Entrapment neuropathies of the median, ulnar, or peroneal nerves are common. Rarer mononeuropathies with abrupt painful onset followed by weakness and atrophy are caused by nerve infarction from occlusion of *vasa nervorum*; two or more nerves may be involved sequentially (multiple mononeuropathies, alias mononeuritis multiplex).

Truncal Radiculopathy is usually unilateral, may affect spinal roots from T4 through T12 and manifests with pain and dysesthesias possibly associated with bulging of abdominal muscles and focal anhidrosis.

- *Pathophysiology* of DSP and SFN remains controversial and the dysmetabolic process (hyperglycemia leading to production of pro-inflammatory advanced glycation products and to accumulation of polyols and reactive oxygen species with oxidative stress; dyslipidamia) may prevail on the ischemic damage. For LSRP an ischemic damage of the nerves due to an immune-mediated epineurial microvasculitis has been hypothesized (based on nerve biopsies) but not proven. Cranial neuropathies are supposed to be due to microvascular infarcts.

35.2.9.4 Diagnosis

According to the American Diabetes Association, all patients should be screened for DSP at diagnosis of T2DM and 5 years after the diagnosis of T1DM, and at least annually thereafter [41].

DSP Should not be diagnosed on the basis of one symptom, sign, or tests alone. At least two tests [symptoms/signs, nerve conduction studies, quantitative sensory testing (QST) should be done]. The diagnosis is made with a Neurological Disability Score ≥3 and/or a Vibration Perception ≤4/8 at the first metatarsal head by the Rydel-Seiffer tuning fork. NCS demonstrates a generalized, symmetric sensory > motor polyneuropathy that is primarily axonal.

SFN Routine electrodiagnostic tests are normal but should be done to rule out subclinical involvement of large fibers. Quantitative sudomotor axon reflex testing (QSART) assesses the sudomotor autonomic function. Skin biopsy is more sensitive (sensitiveness 88 %) than QSART evidencing the reduction of intraepidermal nerve fiber density [42].

Autonomic Neuropathy History and examination may be ineffective for early detection of cardiovascular autonomic neuropathy (CAN). CAN may be suggested by resting tachycardia (> 100 bpm) and orthostatic hypotension (fall in systolic blood pressure >20 mmHg upon standing) without appropriate heart response. At least three relatively easy tests are recommended to assess CAN at the diagnosis of T2DM and 5 years after the diagnosis of T1DM: postural blood pressure testing; heart rate response (HRV) to the Valsalva maneuver with analysis of the R-R intervals. Gastroparesis should be investigated in patients with erratic glucose control. Bladder function should be investigated in patients with recurrent urinary infections, incontinence, palpable bladder. *LSRP* – EMG discloses low femoral-nerve CMAP, prominent fibrillation potentials in thoracic and lumbar paraspinal muscles, and active denervation in affected muscles. CSF proteins are usually mildly increased. Erythrocyte sedimentation rates (ESR) may be increased. MRI of lumbar spine and lumbosacral plexus may rule out structural radiculoplexopathies and demonstrate signs of inflammation.

35.2.9.5 Top Differential Diagnosis

Neuropathies not-related to DM may include: CIDP, systemic vasculitides, alcoholic neuropathies, and other miscellaneous polyneuropathies, mononeuropathies, or radiculopathies [43].

Most frequent non-diabetic causes of DSP after prediabetes and DM (prediabetes and DM account for more than half of DSP cases) include vitamin B12 deficiency, thyroid dysfunction, alcohol, chemotherapy. Even after careful tests, DSP remains "idiopathic" in more than one-fourth of cases [44].

Non-diabetic length-dependent SFN: connective tissue disease, dysthyroidism, vitamin B12 deficiency, paraproteinemia, HIV infection, hepatitis C virus infection, celiac disease, neurotoxic drug exposure; idiopathic.

Autonomic neuropathy: Hereditary amyloidosis. AL amyloidosis. Sjögren syndrome [test for anti-Ro (SSA) and anti-La (SSB) antibodies; autonomic neuropathy may be present with normal serological tests]. Idiopathic immune-mediated autonomic neuropathy (test for nicotinic ganglionic acetylcholine receptor antibodies, present in some patients). Paraneoplastic autonomic neuropathy (test for the most prevalent anti-Hu antibodies and type 2 Purkinje-cell antibodies and collapsing response mediator protein 5). HSAN.

Other asymmetrical/focal and multifocal radiculo-neuropathies: entrapment neuropathies, systemic or non-systemic localized vasculitides, traumatic radiculopathies, neoplastic or infectious polyradiculoneuropathies, compressive radiculopathies, idiopathic plexopathies. Spinal stenosis is common in diabetic patients and should be distinguished from LSRP.

35.2.9.6 Prognosis and Therapy

DSP is slowly progressive and can stabilize or improve with tight control of diabetes.

Neuropathic pain occurs in about 40–60 % of patients, representing one of the most disabling symptoms. Neuropathy is one of the three major risk factors for falls in diabetic patients (together with retinopathy and vestibular dysfunction).

Trophic changes of the distal lower limbs and foot ulcers are a common, potentially severe, complication which is both neuropathic and ischemic in nature, related to unperceived trauma. Foot ulcer decreases the quality of life and increases the risk of lower-extremity amputations and mortality; its prevalence ranges from 2 to 15 %.

Neuropathic osteoarthropathy is a complication of long-standing diabetic neuropathy, characterized by painless fractures of the metatarsal bones and disruption of the metatarsophalangeal joints. Infection of the neuropathic ulcers can lead to chronic osteomyelitis.

Prevention and treatment require an optimum glycemic control. Pancreas transplantation may stabilize or improve the underlying neuropathy. Symptomatic treatment is devoted to pain control. Prevention and treatment of "diabetic foot" is important and usually administered in "foot clinics." Commonly used oral antioxidant agents such as α-lipoic acid demonstrated limited efficacy on neuropathic symptoms and neurophysiological parameters; other available drugs ("pathogenetic treatments") such as aldose reductase inhibitors gave inconclusive results in clinical trials.

Treatment-Induced Neuropathy is an apparently rare, acute, painful neuropathy with allodynia, which may be precipitated by poor metabolic control (ketoacidosis) or by initiation of treatment with insulin and sudden achievement of glycemic control ("insulin neuritis"). In young adults with T1DM it may be associated with cachexia and depression. Pain has marked nocturnal exacerbations and may persist for weeks or months before spontaneous resolution.

Autonomic Neuropathy CAN may limit exercise capacity and increase the risk of adverse cardiovascular events during exercise. Patient with CAN may have difficulties with thermoregulation and should be advised to avoid exercise in hot or cold environments and stay hydrate. CAN gives an increased risk of silent myocardial ischemia and mortality [45]. If the first evaluation is negative for CAN, the screening tests should be repeated annually; if positive, additional cardiovascular tests and symptomatic treatments should be ensured.

LSRP After progressing over several weeks or months, LSRP stabilizes (monophasic, self-limiting evolution); spontaneous pain may decrease rapidly, but prolonged morbidity often ensues. Long-term prognosis seems not to be influenced by glycemic control [46]. There is no evidence from any trial to show whether immunotherapies (IVIg, oral prednisone, or intravenous steroids) are effective [47], but small retrospective studies indicated that IVIg, oral prednisone, or intravenous methylprednisolone are effective, particularly in pain control allowing physical therapy. IVIg should be weighed with the increased risk of renal failure in diabetics. Insulin/oral hypoglycemic drugs should be adjusted during short courses with steroids.

Cranial Neuropathies Usually resolve over several months.

35.2.10 Carpal Tunnel Syndrome (CTS)

Key Facts	
• **Terminology and definitions** – CTS: mono-neuropathy due to median nerve compression in the wrist. • **Clinical features** – Pain, paresthesias, and late atrophy in the median nerve distribution of the hand. • **Diagnostic markers** – **Neurophysiology** – Prolonged median distal sensory and/or motor latencies.	• **Top differential diagnoses** – Cervical radiculopathies, proximal median nerve lesions. • **Principles of treatment** – **Conservative**: wrist splints, FANS, oral or locally injected steroids. – **Surgery**: section of transverse carpal ligament • **Disability** – Spontaneous improvement in 30 % of patients; surgery may obtain almost complete healing in 80–95 % of CTS.

35.2.10.1 Definition

Carpal tunnel syndrome (CTS) is a mononeuropathy due to median nerve compression in the wrist.

35.2.10.2 Epidemiology

With a prevalence of 1/1,000 CTS is the most frequent entrapment mono-neuropathy. The risk of developing CTS is higher in women aged 50–55 years. Usually mild and self-limited forms of CTS affect 20 % of pregnant women. Diabetes, obesity, thyroid, kidney diseases, rheumatoid arthritis, and hand stress are further risk factors.

35.2.10.3 Clinical Features

Pain, tingling, sensory deficits over the median nerve distribution of the hand, provoked or worsened by sleep, alleviated by changing posture or by shaking of the hand, are typical. Atrophy of the thenar eminence is a late sign. Notwithstanding a high proportion of false positive and false negative results, Tinel and Phalen tests are very useful clinical tools for the diagnosis.

35.2.10.4 Diagnostic Markers

Neurophysiology – Median-ulnar palmar sensory latency difference >0.5 msec (distance of 8 cm), or prolonged median nerve Distal Motor Latency >4 msec (mean value + 2 SD).

Ultrasound (US) – besides supporting the diagnosis of idiopathic CTS [increased cross sectional area (CSA) proximal to the compression point where the nerve suddenly flattens (notch sign), and changes of echotexture], US may help individuate causes of secondary CTS often susceptible to therapeutic options.

35.2.10.5 Differential Diagnosis

Cervical radiculopathy, proximal median nerve lesions, brachial plexopathies

35.2.10.6 Therapy

Conservative Opinion differs as to conservative treatment of CTS. Wrist splints reduce hand stress and can give some improvement. There is no evidence that non-steroidal anti-inflammatory drugs are useful. Oral steroids are not as effective as their local injections. Injections of a local anesthetic can relieve symptoms in the short term.

Surgery The section of transverse carpal ligament is the most appropriate therapy if pain and sensory impairment persist after conservative treatment.

35.2.10.7 Prognosis

CTS symptoms and pain tend to decrease with time. One-third of patients have spontaneous improvement.

Fifty-one to 94 % of patients respond initially to a single local steroid injection but after 1 year the percentage of symptom-free patients drops to only 6.5–33 %, whereas over 80–95 % of surgically treated patients result asymptomatic. Pain and weakness usually disappear within 2 months after operation, but it may take 6 months to a year to recover [48].

The prognosis of CTS is worse in the presence of muscle atrophy.

Duration of symptoms, bilateral CTS, positive Phalen test, age (the odds of improvement are reduced by 30 % for each 10 additional years) all are negative prognostic factors [49].

On the contrary, the duration of symptoms is inversely related to improvement of pain notwithstanding a possible progressive worsening of the electrophysiological pattern, symptoms and pain do not increase as the neurophysiological severity progresses.

The presence of hand stress at onset is associated with higher odds of improvement, due to its relief.

35.2.11 Bell Palsy

Key Facts

- **Terminology and definitions** – peripheral, unilateral facial palsy of subacute onset.
- **Clinical features** – subacute, unilateral weakness of an upper and lower emi-face.
- **Diagnosis**
  - **Genetics** – Autosomal dominant transmission is detected in some families.
  - **Imaging** – May show seventh nerve contrast enhancement.
  - **Neurophysiology** – Denervation of affected muscles.
- **Top differential diagnoses** – *central palsies*; *autoimmune neuropathies.*
- **Prognosis**
- **Principles of treatment** – Steroids.
- **Disability** – Healing occurs within 6 months in 80 % of patients; 15 % of cases display moderate or severe residual deficits.

35.2.11.1 Definition

Bell palsy (syn.: facial/seventh nerve palsy, paralysis a frigore) is a peripheral, unilateral facial palsy of subacute onset (2–5 days).

35.2.11.2 Epidemiology

Incidence: 20–30 per 100,000 per year that peaks at age 40–49 years [50].

35.2.11.3 Clinical Features

Unilateral weakness of an upper and lower emi-face with widening of the palpebral fissure, drooping of corner of mouth, inability to smile and close the eye on the affected side. Palsy is complete in 70 % of patients, pain is present in 60 %, taste changes in 30–50 %, and hyperacusis in 15–30 %.

Herpes simplex virus (HSV) infection is the most common cause.

Laboratory Non-significant in isolated palsy

Genetic Autosomal dominant transmission is detected in some families.

Neurophysiology EMG: denervation of affected muscles. The ipsilateral blink reflex is abnormal

Brain MRI May show seventh nerve contrast enhancement and excludes central causes.

Differential Diagnosis Seventh nerve palsy of different origin.

Therapy

Corticosteroids (prednisone 1 mg/kg for 5 days) should be started in the first 72 h from the onset and tapered within 10 days.

Antivirals are usually considered in severe and moderate cases (7-day cycle of: valaciclovir 1 g×2/day, or famciclovivir 750 mg×3/ day, or acyclovir 400 mg 5×/day), but acyclovir, added to corticosteroids, does not provide additional benefit [51].

35.2.11.4 Surgery

Its efficacy is queried. Seventh nerve decompression may be performed in severe palsies that do not make progress. To avoid irreversible nerve degeneration, patients should be operated on within the first 2 weeks from the onset.

35.2.11.5 Prognosis

Bell palsy is a self-limited, monophasic disorder that may recur in 8 % of cases. Healing occurs within 6 months in 80 % of patients; 15 % of cases display moderate or severe residua. Onset of improvement usually takes from 10 days to 2 months and reaches its plateau between 6 weeks and 9 months. Nerve regeneration may require more than 6 months so 15 % of remissions occur in 3–6 months. Facial emispasm is a residual disorder in 17 % of cases.

Weakness has better evolution in patients with: 1 – incomplete paralysis, 2 – early improvement, 3 – younger age, and 4 – timely treatment ($\leq$ 3 days).

Poor prognostic factors include A – age over 60 years, B – hypertension, C – impairment of taste, and D – complete palsy.

Moreover: 1 – absence of improvement at 3 weeks *carries poor prognosis*. 2 – About 90 % of patients fully recover if nerve excitability is maintained at 3 weeks. 3 – Only 20 % recover if nerve excitability has been lost within the same period of time [50]; 4 – from 80 to 100 % of patients regain optimal facial mobility if nerve degeneration is lesser than 90 %. This percentage drops to 50 % if nerve degeneration is equal or greater than 90 %.

35.2.12 Peripheral Nerve Injury (PNI)

Key Facts

- **Terminology and definitions** PNI is a disruption of anatomo-functional integrity of the nerve.
- **Clinical features** PNI occurs in 2–5 % of patients admitted to Level I trauma centers.
- **Diagnostic markers**
  - **Laboratory** – Non-significant.
  - **Imaging** – Ultrasonography and MRI have a role in the diagnostic work-up.
  - **Neurophysiology** – Provides essential information in the diagnosis and management of PNI.
- **Top differential diagnoses** – Acute inflammatory demyelinating polyradiculoneuropathy; cervical spondylosis; diabetic neuropathies.
- **Prognosis**
  - **Principles of treatment** – Symptomatic; surgical repair.
  - **Disability** – *Neurapraxic* lesions usually recover within a few months. In complete *axonotmesis,* recovery is determined by axonal regeneration; in *2nd degree axonotmesis* recovery is complete; in *3rd and 4th* degrees prognosis for spontaneous regrowth is worse.
- **After surgery**: the sooner the nerve is repaired the better the functional recovery will be; recovery is better in young people.

Key Facts

35.2.12.1 Definition and Basic Injury Types

Peripheral Nerve Injury is a total or partial disruption of anatomo-functional integrity of the nerve resulting from kinetic energy applied to the nerve or limb, as in stretch-related injury, laceration and penetrating trauma, or direct compression of a nerve.

Stretch-related injuries are the most common type. Elongation more than 10–15 % produces nerve ischemia and, beyond the limit of elasticity, a complete loss of continuity may occur. *Compression* is also common and includes acute compression as in 'Saturday Night palsy' and chronic compression as in entrapment neuropathies. A dose–response relationship between the duration of compression and neural injury was noted.

35.2.12.2 Demographics

PNI occurs in 2–5 % of patients admitted to Level I trauma centers [52]. In peacetime, young men are mainly affected (range 15–45 years, ratio M/F = 3:1). PNI commonly results from vehicle accidents (about 50 %); iatrogenic factors account for 10–15 % of cases.

PNI classification (Table 35.2)

The extent to which the axons and the connective sheaths of a nerve are disrupted by injury is fundamental to make the prognosis and treatment strategy.

Seddon (1943) proposed three main grades of nerve injury (see Table 35.2) [53]

Sunderland (1978) added two subclasses to Seddon's axonotmesis grade, depending on the degree of connective tissue involvement (see Table 35.2) [54].

In *grade 3* lesions there is endoneurial disruption, while perineurium and epineurium are preserved. Endoneurial discontinuity prevents full spontaneous reinnervation, rarely to more than 60–80 % of normal function. Surgical repair is required in patients with poor functional recovery.

In *grade 4* lesions the internal structure (axons and connective) is completely disrupted, nerve continuity is maintained by epineurium and scar tissue. The internal scarring blocks the regenerating axons (*neuroma in continuity*). Reinnervation occurs only with surgical repair.

35.2.12.3 Nerve Response to Injury

Remyelination: is the early and faster mechanism to promote recovery

Collateral sprouting: in partial axonotmesis, muscle strength may recover thanks to collateral sprouting from distal intact axons.

In 4th and 5th degree injuries (Table 35.2) the scar tissue prevents the regenerating axons from reaching the distal routes, leading to the formation of a *neuroma-in-continuity* in 4th degree injury and an *amputation neuroma* in 5th degree injury.

35.2.12.4 Neurophysiology

It provides essential information in the diagnosis and management of PNI by:

Table 35.2 PNI classification

Seddon	Sunderland Grade	Pathology	Prognosis	Electrophysiological correlate
Neuroapraxia	1	Myelin injury and/or ischemia usually secondary to compression	Excellent recovery in weeks to months	Conduction block complete or partial ± conduction slowing across the site of lesion
Axonotmesis	2	Axon loss; stromal derangement; endoneurium, perineurium, and epineurium intact	Good spontaneous regeneration	FP; mild reduction to absence of SNAP and CMAP in relation to the degree of axonal loss ± varying degree of slowing and block of conduction
	3	Loss of continuity of axons and endoneurium; perineurium and epineurium intact	Variable reinnervation, axonal misdirection, surgery may be required.	FP, absent SNAP and CMAP
	4	Loss of continuity of axons, endoneurial tubes, perineurium and fasciculi; epineurium intact	Internal scar tissue blocks regenerating axons (neuroma in continuity). Surgery required	FP, absent SNAP and CMAP
Neurotmesis	5	Loss of continuity of entire nerve trunk	No spontaneous recovery, need of surgical repair	FP, absent SNAP and CMAP

FP fibrillation potential, *SNAP* sensory nerve action potential, *CMAP* compound muscle action potential

1. *Localizing the site of nerve injury*. The site of nerve conduction failure may be detected within the first week, then it is lost in the case of axonal discontinuity. Persistence of SAP in the face of sensory loss invariably means that the lesion is proximal to the dorsal root ganglion.
2. *Discriminating neuroapraxia from axonotmesis and quantifying the degree of axonal loss* (after 2–3 weeks post-injury).
3. *Recognition and measurement of reinnervation* (after 3–4 months post injury). Early reinnervation may be detected in the muscle proximal to the lesion site by recording the voluntary recruitment of a few small MU, before clinical evidence.

Ultrasound (*US*) *and magnetic resonance* (*MRI*) imaging have a role in the diagnostic work-up in PNI.

High-resolution US may strongly modify the diagnostic process and therapeutic strategies in patients with PNI [55].

Magnetic resonance (*MRI*) is uniquely informative in the diagnosis of avulsions that frequently occur in closed traction injury of the brachial plexus [56].

35.2.12.5 Prognosis

Factors affecting prognosis are:

- *Clinical severity of PNI*. Complete loss of temperature-pain detection and of autonomic responses invariably indicates a severe PNI. The Medical Research Council (MRC) method of recording muscle power and sensibility offers a practical tool to make a grading of the PNI and to measure the progress.
- *Type of PNI. Neurapraxic lesions* have a good prognosis for recovery within a few months. *Mixed nerve injuries* typically have two phases of recovery: the neurapraxic component resolves quickly, but the axonal component is slower, because it depends upon axonal sprouting and the distance to reach the target. With lesions involving less than 20–30 % of the axons, recovery occurs over 2–6 months predominantly by collateral sprouting from intact axons.
- In *complete axonotmesis,* recovery is determined uniquely by axonal regeneration, which occurs depending upon the degree of PNI. In 2nd degree injury, recovery is complete and can be planned considering the rate of axonal growth (about 1–5 mm/day). The CMAP amplitude provides some guide to prognosis. In the 3rd and 4th degrees, prognosis for spontaneous regrowth is worse. Extensive scarring reduces the growth rate of regenerating axons and their ability to cross the lesion to reach the end organs. Since it is not possible to know the degree of axonotmetic lesions on the basis of preoperative data, it is necessary to look for reinnervation in proximal muscles after 2–4 months. Lesions with some spontaneous recovery are usually treated conservatively, while absence of reinnervation requires operative exploration. *Neurotmesis* requires surgical repair.
- *Level of injury*: distance from the lesion site to the end organs determines the functional outcome. Proximal lesions such as root avulsion, lumbar-sacral plexus and sciatic nerve injury have bad prognosis. Root avulsion cannot be surgically repaired.
- *Delay in diagnosis and surgery*: the sooner the nerve is repaired the better the functional recovery will be. Muscle reinnervation must occur within 12–18 months (before fibrotic replacement), while sensory recovery may continue for a longer period of time.
- *Age*: recovery is better in young people; older patients are more likely to develop pain.
- *Abnormal Reinnervation*: muscle co-contraction is particularly common in brachial plexus injury.
- *Vascular injuries*, *post-ischemic contracture*, *tendon retraction and muscle fibrosis*, *stiffness of joints* all are negative prognostic factors.

35.2.12.6 Therapy

Symptomatic management. Control of *neuropathic pain* [57]:

- Mild pain (VAS <5) can be treated with NSAIDs.
- Topical lidocaine patches are very useful in localized cutaneous pain

- In severe pain (VAS more than 5–6) use low-dose tricyclic agents such as nortriptyline or antiepileptic drugs (gabapentin/pregabalin, lamotrigine, and carbamazepine).
- Patients unresponsive to these agents may require narcotic analgesia. First, it may be used tramadol, and if ineffective, oxycodone with increasing doses for not more than 3–4 months (studies on long-term efficacy, safety and effects on quality of life are lacking).
- Spinal cord or nerve stimulators may be useful for patients with segmental neuropathic pain.

Patients with weakness and deformity should be considered for physical and occupational therapy evaluation. Use appropriate assistive devices such as cock-up wrist splints for radial nerve injuries and AFO splints for foot drop. Consider muscle and tendon transfer to improve residual function in selected cases.

Surgical nerve repair is indicated in 4th or 5th degree injury. *Primary repair* is performed immediately or within 1 month (delayed primary repair) and *secondary repair* is performed at between 3 weeks and 3 months after injury [58].

Immediate end-to-end repair is performed in nerve transection due to sharp lacerations. Delayed primary repair in blunt trauma or avulsion requires nerve grafting, as the nerve ends are usually retracted and/or scars need to be resected. Nerve autografts (sural nerve) remain the gold standard.

Secondary repair is preferred when the degree of injury has not yet been ascertained. Surgical procedure is recommended in absence of reinnervation in the proximal muscles within 3–4 months from injury, as the quality of motor recovery decreases steadily after a 6-month delay of repair.

Late nerve reconstruction, beyond 6 months, is generally carried out for pain control, such as neuroma resection.

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Disorders of Autonomic Nervous System

36

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Abbreviations

AD, Alzheimer's disease; ADL, activity of daily living; AF, autonomic failure; ANS, autonomic nervous system; BP, blood pressure; CNS, central nervous system; DBP, diastolic blood pressure; DLB, dementia with Lewy bodies; FD, familial dysautonomia; HSANs, hereditary sensory and autonomic neuropathies; HUT, head-up tilt; MSA, multiple system atrophy; NOH, neurogenic orthostatic hypotension; OH, orthostatic hypotension; PAF, pure autonomic failure; PD, Parkinson's disease; PNS, peripheral nervous system; PoTS, postural tachycardia syndrome; SBP, systolic blood pressure

Key Facts

- **Terminology and definitions** – Orthostatic hypotension (OH) is a sustained reduction of systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of 10 mmHg within 3 min of standing or head-up tilt.
- **Epidemiology and clinical features** – OH range between 5 and 30 % in aged population. *Neurogenic OH* may be primary or secondary to neurodegenerative diseases (α-synucleinopathies). Symptoms include light-headedness, visual disturbances, and syncope.
- **Diagnostic markers** – Autonomic testing (including HUT, valsalva manoeuvre, etc..)
  - **Blood** – Supine and standing noradrenaline plasma level
  - **Imaging** – Myocardial imaging with ^{123}I-metaiodobenzylguanidine scintigraphy
- **Top Differential Diagnoses** – Dehydration, acute blood loss, drugs
- **Prognosis**
  - **Medical therapy** – *Non-pharmacological* and pharmacological approaches
  - **Disability** – Autonomic failure plays a negative prognostic role in α –synucleinopathies. OH from any causes increases the risk of stroke, myocardial ischemia, heart failure, and all-cause mortality, both in middle aged and elderly individuals.

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36.1 Introduction

Among the many disorders affecting the autonomic nervous system (ANS), we will discuss the prognosis of neurogenic orthostatic hypotension (NOH), familial dysautonomia (FD), and postural tachycardia syndrome (PoTS). NOH is often associated with neurodegenerative disorders called α-synucleinopathies that primarily affect the ANS and represents a negative prognostic factor, increasing mortality and morbidity. NOH is also linked to an increased risk of cardiovascular and cerebrovascular events in the general population, especially in the elderly. FD, also known as Riley-Day syndrome, severely affects patients from childhood. Encouragingly, in the last decades the prognosis has greatly improved, with a life expectancy of more than 40 years for most patients. PoTS has usually a favorable prognosis, however, the remitting and relapsing clinical course associated with moderately severe symptoms can affect the quality of life, as patients may experience difficulties with daily routines, work, and social life.

36.2 Neurogenic Orthostatic Hypotension (NOH)

36.2.1 Terminology and Definitions

Orthostatic hypotension (*OH*) is a sustained reduction of systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) within 3 min of standing or head-up tilt (HUT) to at least 60° on a tilt table. Since the magnitude of BP drop also depends on baseline values, it was suggested that a drop of 30 mmHg may be a more appropriate criterion for OH in patients with supine hypertension. OH is caused by an inability of the autonomic nervous system (ANS) to adapt to the demands of upright posture, resulting in defective vasoconstriction and excessive pooling of venous blood.

Delayed OH is a variant of OH, which occurs beyond 3 min. It should be suspected in patients who do not exhibit OH at bedside, but complain of OH symptoms on prolonged standing.

Initial OH in some cases may occur within 15 s of standing. Initial OH represents a transient mismatch between cardiac output and peripheral vascular resistance rather than autonomic failure.

OH may be caused by several conditions, not necessarily by a structural damage of the ANS. Medications that cause excessive vasodilatation, hypovolemia, cardiac pump failure, and venous pooling are frequent causes of inadequate autonomic control, which results in secondary OH.

When OH is caused by a primary abnormality of the ANS, or autonomic failure (AF), it is defined as *neurogenic* orthostatic hypotension (NOH). As the ANS innervates the whole body, NOH is frequently accompanied by other symptoms of autonomic dysfunction in other organs and systems, including urogenital, gastrointestinal, respiratory, and sudomotor functions. Autonomic dysfunction may be part of neurodegenerative diseases (primary autonomic failure), such as multiple system atrophy (MSA), Parkinson's disease (PD), dementia with Lewy bodies (DLB), and pure autonomic failure (PAF), which are collectively called α-synucleinopathies. AF could also be secondary to autonomic neuropathies as in diabetes, amyloidosis, and other systemic disorders. Traumas, tumors, and other types of degeneration of the central nervous system (CNS) may also be associated with AF and, therefore, NOH.

In this chapter we will consider only NOH due to primary autonomic neurodegenerative disorders that may affect the central or peripheral autonomic pathways.

36.2.2 Demographics

No epidemiological studies have taken into account the difference between NOH and secondary OH when estimating the prevalence of this condition and thus we only have cumulative data.

In the general aged population, the prevalence rates of OH range between 5 and 30 %. The difference is due to the composition of the population studied (age range, institutions, healthy population versus selected groups), the influence of medications, and the level of orthostatic stress [1]. The prevalence of OH increases significantly with age and in institutionalized patients, and it likely reflects the presence of multiple risk factors such as comorbidities and medications in these subjects. Moreover, some epidemiological studies may have underestimated the prevalence of OH, since they were based on the identification of symptoms of OH rather than systematic measurement of SBP or DBP drop upon standing. In fact, patients with long-standing OH may lack orthostatic symptoms thanks to compensatory changes that ensure adequate cerebral perfusion even during a severe drop in BP.

The prevalence of NOH in α-synucleinopathies is as follows: MSA 75 % [2], PD 30 % [3], DLB 30–50 % [4], and PAF 100 % [5]. All these disorders, with the exception of PD, are very rare.

36.2.3 Clinical Features

The clinical presentation of NOH varies from asymptomatic to an invalidating condition that severely affects the quality of life. Symptoms are mainly due to cerebral hypoperfusion and include light-headedness, dizziness, visual disturbances, and syncope. Symptoms may also be aspecific, such as generalized weakness, leg buckling, or headache. Pain in the neck and shoulders ("coat hanger pain") due to ischemia of local muscles is very typical. Symptoms do not necessarily occur immediately after standing up but invariably disappear when the patient lies down.

Post-exercise hypotension, postprandial hypotension and supine hypertension are quite common in patients with NOH.

36.2.4 Diagnostic Markers

NOH is very easy to detect, but it does not add any information about the underlying cause. Therefore, the following investigations are often required, and usually a combination of the results can point toward a more defined diagnosis.

36.2.4.1 Neurophysiology

The diagnosis of OH requires a measurement of a drop in SBP of at least 20 mmHg and/or a drop in DBP of 10 mmHg within 3 min after standing up. Passive HUT is a valid option. In patients with NOH, HUT is not sufficient to determine whether it is due to a central or peripheral disorder. Further autonomic testing includes functional assessments of the parasympathetic nervous system (e.g., heart rate variability with deep respiration and during Valsalva maneuver), the sympathetic cholinergic system (e.g., thermoregulatory sweat response and quantitative sudomotor axon reflex test), and the sympathetic adrenergic system (e.g., blood pressure response to Valsalva maneuver).

36.2.4.2 Laboratory

Supine and standing noradrenaline plasma level: to discriminate the central versus peripheral autonomic dysfunction. Pharmacological probes (e.g., noradrenaline, isoprenaline, tyramine, clonidine, and edrophonium) may be used.

36.2.4.3 Imaging

Myocardial innervation imaging using ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy: to distinguish peripheral from central NOH.

Cardiac noradrenergic denervation always occurs in PD + NOH. This finding suggests that in PD dysautonomia is peripheral, as well as in PAF and DLB. Patients with MSA usually have intact innervation, suggesting a central dysfunction of the ANS. Therefore, cardiac MIBG scintigraphy may be used in the diagnostic work-up of patients, especially to differentiate PD + NOH from MSA with predominant Parkinsonian features.

36.2.5 Top Differential Diagnosis

- Dehydration and acute blood loss
- Drugs (e.g., antihypertensive agents and antidepressants)
- Reduced cardiac output (e.g., constrictive pericarditis, cardiomyopathy, and aortic stenosis)
- Endocrine disorders (e.g., adrenal insufficiency and pheochromocytoma)
- Excessive vasodilatation (e.g., systemic mastocytosis and the carcinoid syndrome)

36.2.6 Principles of Treatment

Current guidelines on the treatment of NOH are available in literature [6–8].

A combination of non-pharmacological and pharmacological approaches is often necessary.

Mild physical activity to avoid deconditioning and multiple smaller meals to prevent postprandial hypotension are also recommended, as well as a diet high in salt (10 g of sodium) and plenty of fluids (2–2.5 L) to maintain plasma volume. Medications that can cause or exacerbate OH should be discontinued or reduced; it may be necessary in these cases to accept some supine hypertension in order to maintain orthostatic tolerance.

Pharmacological treatment acts through two possible mechanisms: vasoconstriction and intravascular volume expansion. Midodrine is a sympathomimetic drug currently approved for the treatment of NOH in the US and Europe, whereas all other drugs are restricted to off-label use. Fludrocortisone is also widely used; it is a synthetic mineral corticoid that increases plasma volume by renal sodium retention.

36.2.7 Prognosis

Patients with MSA have a poor prognosis of survival: less than 9 years on average; autonomic dysfunction is consistently associated with poor health-related quality of life [9, 10].

Early development of autonomic dysfunction has been proven to be an independent risk factor for rapid disease progression and shorter survival.

Patients who developed AF in the first 2.5 years of MSA were in a wheelchair-bound state, and in a bedridden state, and died after 2.5, 3.5, and 5.5 years, respectively. These times were significantly delayed for patients who developed AF after 2.5 years (5.5, 6.0, and 9.5, respectively).

Early development of autonomic dysfunction also increased the risk of sudden death, with a hazard ratio of 7.22 [11].

Recently, cases of long-term MSA with a survival of more than 15 years have been described, and all these cases presented with late occurrence of dysautonomia. The emergence of late cardiovascular autonomic failure (on average 11.3 years after motor symptom onset) heralded a second phase of more rapid disease deterioration analogous to that seen in typical cases of MSA, with a mean duration of the second phase of illness of 5.7 years [12, 13].

In PD, autonomic dysfunction has been found to be more common in patients with falls and fractures, and it is an independent predictor of earlier falls. As falls and fractures contribute to morbidity and mortality in bradykinetic rigid syndromes, this finding further supports the notion that autonomic dysfunction is linked with a more aggressive disease process. Like other non-motor symptoms of PD, autonomic dysfunction severely affects the quality of life.

Autonomic dysfunction in DLB occurs early in the clinical course and has an intermediate severity compared to MSA (which is the most affected) and PD (which is the least severely affected) [4]. Moreover, the latency from onset of disease to OH seems to be delayed in DLB compared to MSA and PD [4]. OH has been found to be a possible independent predictor of shorter survival in DLB. The Kaplan-Meier curve (Fig. 36.1) shows the influence of OH on survival in patients with DLB. Patients with persistent OH had a significantly shorter survival. Other features of autonomic dysfunction (urinary incontinence and constipation), in addition to persistent OH, had an additional negative effect on survival (Fig. 36.2) [14].

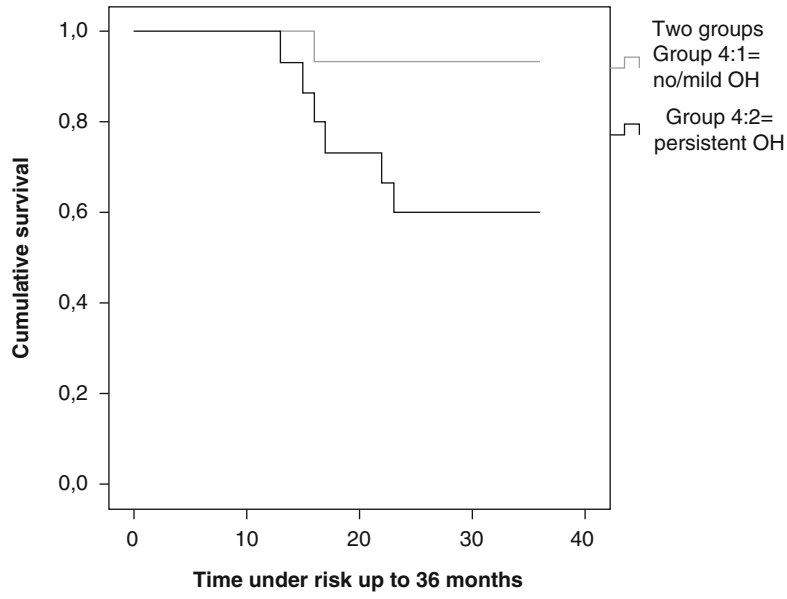

Fig. 36.1 Orthostatic hypotension and survival. This Kaplan-Meyer curve shows that patients with persistent orthostatic hypotension have a significantly shorter survival rate compared to those with no or mild orthostatic hypotension (Reproduced from Stubendorff et al. [14], copyright 2014])

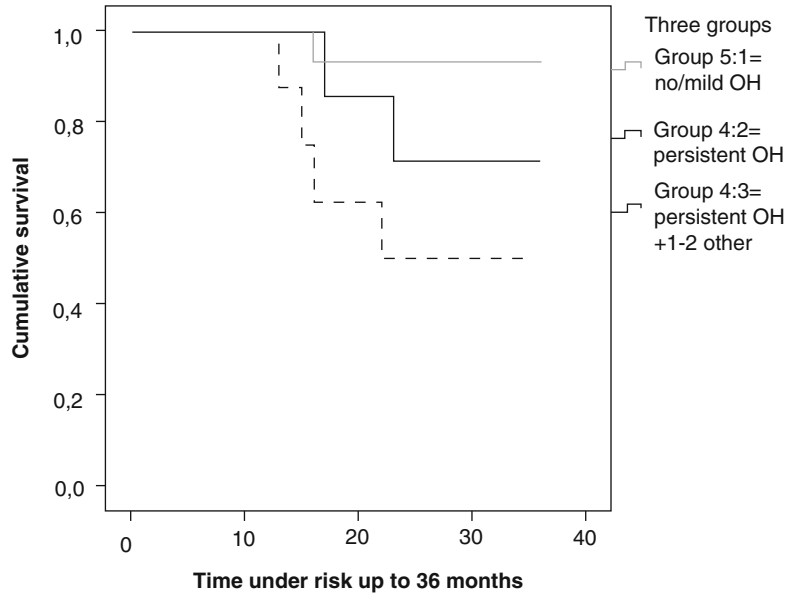

Fig. 36.2 Manifestation of autonomic dysfunction and survival. This Kaplan-Meyer curve shows that the presence of concurrent manifestations of autonomic dysfunction, that is, constipation and urinary incontinence, in addition to persistent orthostatic hypotension, has an additional negative effect on survival (Reproduced from Stubendorff et al. [14])

Importantly, demented patients may not show significant falls in BP until as late as after 10 min; measurements of BP should therefore be recorded for at least 10 min after standing up. Some studies comparing DLB to Alzheimer disease (AD) report a similar rate of cognitive decline but patients with DLB have an increased risk of mortality when compared to AD patients. In fact, mean age at death for DLB patients was 78.0 years compared with a median age at death of 84.6 years for AD patients and survival after dementia onset was also different between DLB and AD (7.3 vs. 8.5 years). Patients with DLB have a shorter time to institutionalization than patients with AD (70% vs. 51% patients institutionalized after 58.91 ± 35.2 months of follow up) [15]. Patients with DLB also report a more impaired quality of life compared to

AD. Autonomic dysfunction may be one of the contributing factors to these differences [14].

PAF is characterized by isolated AF with prominent OH in the absence of signs of central or peripheral nervous system disease. In some cases, it could be the initial presentation of other neurodegenerative disorders like PD or DLB [16]; therefore, 5 years should pass before making a definitive diagnosis of PAF.

In patients who present with AF alone, the disorder progresses gradually, with symptoms that respond well to therapy. Therefore, PAF has a better quality of life and prognosis than central autonomic neurodegenerative disorders. PAF patients do not show diminishing capacity for the activity of daily living (ADL) up to a late stage, and live independently until 1 or 2 years before death (Fig. 36.3). This advantage in ADL and long-term prognosis may be due to the fact that they do not usually have severe urinary disturbances (which would be a risk factor for recurrent urinary infections) or life-threatening respiratory failure. Moreover, they respond well to therapy for OH, thus preventing faintness and syncope (which could result in head injuries or bone fractures), and they do not have motor or cognitive impairment [17].

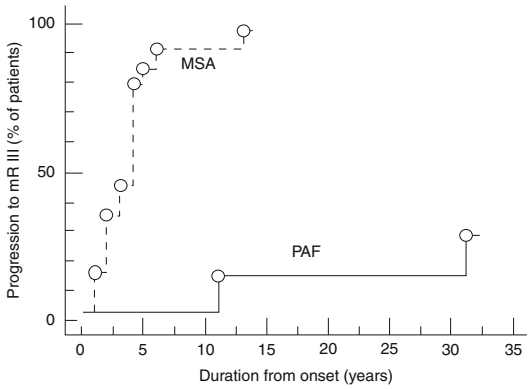

Fig. 36.3 Differences in time remaining independent in activities of daily living between patients with pure autonomic failure (PAF) and multiple system atrophy (MSA) (Reproduced from Mabuchi et al. [17], with permission from BMJ Publishing Group Ltd)

In summary, there is clear evidence that AF plays a negative prognostic role in α-synucleinopathies; therefore, precocious screening and therapeutic management of cardiovascular AF may positively impact disease course.

Mortality and prognosis in a population of patients with NOH associated with MSA, PAF, PD, and autonomic neuropathy have been investigated recently: patients with NOH had a threefold increased risk of mortality with respect to the general population living in the same area with a similar age range and relative to the same period. Main causes of death were infectious/respiratory (54 %), cardiac (16 %), cachexia (9 %), stroke (7 %), cancer (7 %), and trauma (4 %). The type of autonomic neuropathy associated with NOH was confirmed as the main factor for prognosis [18].

Several longitudinal studies in the general population have shown that OH increases the risk of stroke, myocardial ischemia, heart failure, and all-cause mortality, both in middle-aged and elderly individuals. However, none of these studies consider whether OH is due to neurogenic dysfunction or other causes, such as cardiac dysfunction, reduced effective intravascular volume, anti-hypertensive medications or other drugs.

In an elderly cohort, those with OH had a significantly lower 4-year survival rate compared with those without OH, with an age-adjusted mortality rate per 1000 person-years of 56.6 vs. 38.6 [19]. In the elderly, OH might be an indicator of a general lessening of physical strength or frailty. In a middle-aged cohort, a >3-fold increased risk of deaths from all causes was observed among those with OH. This could only be partly explained by age, sociodemographic characteristics, risk factors, and comorbid health conditions, as a 1.7-fold increased risk of death persisted even after adjustment of these factors. A possible subclinical autonomic dysfunction might have been involved [20].

36.3 Familial Dysautonomia (FD)

Key Facts

- **Terminology and definitions** – Familial dysautonomia (FD) is an autosomal recessive disease resulting from poor development and progressive degeneration of the autonomic and peripheral sensory nervous system.
- **Epidemiology and clinical features** – In Israel, the prevalence is 1/3703. Sensory and autonomic dysfunction are progressive and present from birth with gastrointestinal and respiratory dysfunction, lack of overflow tears, profuse sweating, and OH. Perception of pain and temperature stimuli is reduced, with sparing of the palms, soles of the feet, the neck, and genital areas. Taste is inappropriately perceived.
- **Diagnostic markers**
  - **Blood** – Plasma catechol profiling demonstrates diminished sympathetic cardiovascular innervation
  - **Genetics (12)** – *Mutated* IKBKAP gene
  - **Imaging (12)** – Cardiac imaging studies show noradrenergic hypoinnervation
- **Top Differential Diagnoses** – Other HSANs
- **Prognosis**
  - **Medical therapy** – Supportive
  - **Disability** – Newborns have 50 % probability of reaching 40 years of age; quality of life has also improved.

36.3.1 Terminology and Definitions

Familial dysautonomia (FD) is an autosomal recessive disease resulting from poor development and progressive degeneration of the autonomic and peripheral sensory nervous system. It is classified among the hereditary sensory and autonomic neuropathies (HSANs), each caused by a different genetic error.

Synonyms: hereditary sensory and autonomic neuropathy type 3; HSAN type 3; Riley-Day syndrome.

36.3.2 Demographics

FD is a very rare disorder currently confined to the Ashkenazi-Jewish population who lives in Israel and in the greater New York City area. The disease frequency in Israel is estimated to be 1 in 3703, which is higher than that of North American Ashkenazi Jews where the rate is 1/10,000–20,000. Using molecular diagnosis, carrier rates have been found to rate from 1 in 25 to 1 in 42.

36.3.3 Clinical Features

Manifestations of sensory and autonomic dysfunction are present from birth, and the course tends to be progressive. The clinical spectrum includes gastrointestinal dysfunction, abnormal respiratory responses to hypoxic and hypercapnic states, gastroesophageal reflux, vomiting crises, lack of overflow tears, profuse sweating, and OH.

Peripheral sensory system involvement is documented by reduced response to painful stimuli, with sparing of the palms, soles of the feet, the neck, and genital areas. Temperature appreciation is also affected, whereas visceral sensation is intact.

When vomiting is associated with hypertension, tachycardia, diffuse sweating, and personality changes, this constellation of signs has been termed *dysautonomic crisis*, and represents the most debilitating manifestation of autonomic dysfunction in FD.

Cardiovascular autonomic dysfunction with electrocardiographic abnormalities are common, in particular prolongation of the QTc and arrhythmias. Sudden death has also been reported.

Patients with FD are far more likely than the general population to develop chronic kidney disease. Lack of overflow tears and corneal hypoesthesia predispose the cornea to neurotrophic ulcerations. Severe and juvenile kyphoscoliosis is extremely frequent in FD and can be pernicious in its course. Most affected individuals are of normal intelligence, and the behavioral abnormalities that may occur in this disorder tend to be part of the central autonomic dysfunction.

36.3.4 Diagnostic Markers

Clinical diagnosis is based upon the presence of five criteria that are relatively invariable:

- Absence of fungiform papillae on the tongue and decreased taste
- Absence of axon flare after intradermal histamine
- Decreased or absent deep-tendon reflexes
- Absence of overflow emotional tears
- Orthostatic hypotension

With the identification of the genetic mutations causing this disorder, DNA diagnosis is now possible.

36.3.4.1 Laboratory

Blood Plasma catechol profiling when supine and standing presents a distinct, abnormal pattern, consistent with diminished sympathetic cardiovascular innervation.

Genetics The FD gene has been identified as *IKBKAP*, localized in the long arm of chromosome 9 (9q31). This gene encodes for I-k-B kinase complex associated protein, which is deficient in FD. Two Jewish mutations were identified. A third mutation was seen only in one non-Jewish individual, but it was paired with the common mis-splicing Jewish mutation.

Imaging Cardiac imaging studies show noradrenergic hypo-innervation consistent with a postganglionic sympathetic loss.

36.3.5 Top Differential Diagnoses

FD belongs to HSANs, a group of rare disorders caused by an abnormal migration and maturation of neural crest derived cells. Some clinical differences distinguish FD from other HSANs; DNA analysis provides a definite diagnosis.

36.3.6 Principles of Treatment

Management of FD is symptomatic and preventive, when possible: gastrostomy to treat feeding problems; prokinetic agents, H2 antagonists, or surgical intervention for esophageal dysmotility and gastroesophageal reflux; dialysis for renal failure, etc. Dysautonomic crises are treated with diazepam and clonidine when hypertension is severe.

Manipulating protein expression in order to raise the amount of the normal protein product, IKAP, has been suggested as a promising new therapeutic approach.

36.3.7 Prognosis

There has been a great improvement in the prognosis of patients with FD as current survival statistics indicate that a newborn has a 50 % probability of reaching 40 years of age [21], whereas survival statistics prior to 1960 reported that 50 % of patients died before 5 years of age.

Quality of life has also improved. Both men and women with FD have married and reproduced; all offspring have been phenotypically normal despite their obligatory heterozygote state. However, patients report lower physical quality of life as they grow old, with worsening of general health that limits their social role. Therefore, counseling in younger patients, as well as physical and occupational therapy, should be provided in advance of expected lower quality of life [22]. The main complaints are poor balance, unsteady gait, and difficulty in concentrating. Patients are also more prone to depression, anxiety, and phobias. With increasing age, the sympathovagal balance becomes more precarious with worsening of OH, development of supine hypertension, and occasional bradyarrhythmias. Causes of death are usually pulmonary failure, unexplained sudden death, or renal failure [23].

36.4 Postural Tachycardia Syndrome (PoTS)

Key Facts

- **Terminology and definitions** – (PoTS) is a form of chronic orthostatic intolerance, resulting from cardiovascular autonomic dysfunction.
- **Epidemiology and clinical features** – Prevalence 170/100,000; women/men = 4,5/1. Symptoms are orthostatic and very similar to those of NOH: tachycardia, sweating, fatigue, exercise intolerance, and anxiety.
  - **Blood** – Plasma norepinephrine level >600 ng/ml
  - **Genetics** – Twenty percent of patients with adult PoTS syndrome have a family history of orthostatic intolerance
  - **Neurophysiology** – Diagnosis of PoTS requires a sustained heart rate increment of ≥30 beats/min (or ≥40 beats/min in 12–19-year-old individuals) within 10 min of standing. Standing heart rate is often above 120 beats/min.
- **Top Differential Diagnoses** – Chronic fatigue syndrome, orthostatic hypotension,
- **Prognosis**
  - **Medical therapy** – non-pharmacological and pharmacological (ß-blockers, octreotide, ivabradine) approaches
  - **Disability** – Remitting and relapsing clinical course self-resolving in the majority of patients, sometimes with reduction of quality of life

36.4.1 Terminology and Definitions

Postural tachycardia syndrome (PoTS) is a form of chronic orthostatic intolerance, resulting from cardiovascular autonomic dysfunction. PoTS is defined by a sustained heart rate increment of ≥30 beats/min within 10 min of standing or HUT, in the absence of OH.

Patients can experience difficulty with daily routines and pose a particular challenge in management, reflecting the pathophysiological heterogeneity and the presence of multiple comorbidities.

Synonyms: vasoregulatory asthenia, neurocirculatory asthenia, hyperadrenergic orthostatic tachycardia, chronic orthostatic intolerance, orthostatic tachycardia, sympathotonic orthostatic hypotension, hyperadrenergic orthostatic hypotension, hyperdynamic beta adrenergic state, idiopathic hypovolemia, effort syndrome.

36.4.2 Demographics

The prevalence of PoTS is unknown: one estimate is of 170 cases per 100,000 individuals; the true prevalence is likely to be higher since the diagnosis is not easily made.

Commonly, PoTS presents in teenagers within a few years of their pubertal growth spurt, most cases between the ages of 15 and 25 years with relatively few affected patients over the age of 40 years. The syndrome is more frequent in women (4–5:1). Reasons are not known, except for the fact that women are known to be more vulnerable to orthostatic stress.

36.4.3 Clinical Features

PoTS is a clinically heterogeneous condition that can result from a partially denervated circulatory system (impaired sympathetically mediated vasoconstriction), a hyperadrenergic state (excessive sympathetic drive), volume dysregulation, deconditioning, or a combination of those.

Onset can be insidious; often symptoms appear after a period of viral infection (approximately 50 %) or inactivity from illness or injury. Symptoms are linked to orthostatism and are very similar to those described for NOH (see above). They are associated with signs of a hyperadrenergic state (tachycardia, sweating, and tremulousness), with fatigue, exercise intolerance, anxiety, nausea and other gastrointestinal symptoms, acral coldness or pain, dry eyes, inappropriate

sweating, sleep disturbance, concentration difficulties, and headaches.

36.4.4 Diagnostic Markers

Blood Plasma catecholamine measurement, both in supine and during standing or HUT can be of value. In PoTS, there is typically a rise in plasma norepinephrine level (>600 ng/ml), which may be amplified in the subgroup of hyperadrenergic PoTS patients.

Neurophysiology Heart rate evaluation: the diagnosis of PoTS requires a sustained heart rate increment of ≥30 beats/min (or ≥40 beats/min in 12–19-year-old individuals) within 10 min of standing or HUT (60°) in the absence of OH. The standing heart rate is often above 120 beats/min. These criteria may not be applicable for individuals with low resting heart rate.

Further diagnostics are used to determine subtypes as neuropathic PoTS and hyperadrenergic PoTS.

Basic further investigations should include ECG, echocardiogram, Holter monitoring, autonomic reflex testing to detect possible underlying autonomic neuropathy, and measurement of supine and standing plasma catecholamine levels, to assess the baroreflex sympathoexcitation and possible hyperadrenergic PoTS.

Genetics ß2-adrenoreceptor polymorphisms have been described in patients with PoTS. At least 1–2 out of 8 patients with adult PoTS syndrome have a family history of orthostatic intolerance.

PoTS is furthermore associated with a family history of irritable bowel syndrome, migraine headaches, and depressive signs. Hyperextensible joints and known disorders of basic cellular matrix, including Ehlers-Danlos syndrome, are often reported to be linked with PoTS.

Imaging MIBG myocardial scintigraphy has been used to estimate local myocardial sympathetic innervation and function in PoTS. Its diagnostic utility remains to be determined.

36.4.5 Top Differential Diagnosis

- Chronic fatigue syndrome
- Inappropriate sinus tachycardia
- Cardiac rhythm abnormalities
- Orthostatic hypotension
- Central hypovolemia conditions (dehydration, anemia, hyperthyroidism)
- Medication (e.g., vasodilators, diuretics, and β-agonists)
- Panic, anxiety, or somatization disorder
- Central dysautonomias
- Addison disease and pheochromocytoma

36.4.6 Principles of Treatment

Management of PoTS patients requires individualized, non-pharmacological and pharmacological approaches including measures to reduce orthostatic stress and avoid hypovolemia. See section “Principles of treatment in NOH” for main guidelines for treatment of orthostatic symptoms.

Measures to reduce tachycardia consist of ß-blockers, octreotide to prevent postprandial tachycardia, ivabradine for selective sinus node blockade, clonidine for its central sympatholytic effect, and possibly desmopressin for reducing the heart rate. ß2-blockers seem the most effective in PoTS.

36.4.7 Prognosis

PoTS may follow a remitting and relapsing clinical course of moderately severe symptoms and associated fatigue, often enduring for years. However, with appropriate management, the prognosis is favorable, and PoTS appears self-resolving in the majority of patients, especially in those patients with a triggering event, such as a viral illness.

PoTS patients can have trouble with daily routines and are often unable to continue with their work and social activities. The potential economic and social burden is great since the average patient with PoTS is a young, highly educated [24], previously healthy individual, who could be

looking forward to their best years of economic and social productivity.

Patients reported clear limitations in several areas of quality of life, including the physical, social, and functioning domains, in particular energy level and role functioning are affected [25].

The high impairment of quality of life has two main causes. Firstly, simple daily activities such as eating, showering, or low-intensity exercise may profoundly exacerbate symptoms [24]. Secondly, many patients may experience other symptoms not attributable to orthostatic intolerance, such as gastrointestinal or bladder functional disorder, chronic headache, fibromyalgia, and sleep disturbances [25, 26]. Disability is not strictly correlated with the severity of symptoms, suggesting the importance of other psychosocial factors [25].

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Autoimmune Ion Channel Disorders of the Peripheral Nervous System

37

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Abbreviations

AAG, Autoimmune autonomic ganglionopathy; Ab, antibody; Ach, *acetylcholine*; AChR, acetylcholine receptor; AID, Autoimmune ion channel disorders; caspr2, contacting-associated protein 2; AZA, azatioprine; CIP, intestinal pseudo-obstruction; CSR, complete stable remission; CYA, cyclosporine A; CYP, cyclophosphamide; DAP, 3.4 diaminopyridine; ICU, intensive care unit; IVIG, high-dose intravenous immunoglobulins; LEMS, Lambert-Eaton myastenic syndrome; LGI1, glioma inactivated 1 protein; MG, myasthenia gravis; MMF, micophenolate mophetil; MTX, methotrexate; Musk, Muscle-specific receptor tyrosine kinase; NMJ, neuromuscular junction; NMT, Acquired Neuromyotonia; NT-LEMS, non-paraneoplastic LEMS; PLEX, plasma exchange; POTS, postural tachycardia syndrome; RNS, repetitive nerve stimulation; SCLC, small cell lung cancer VGCC, voltage-gated calcium channel; SFEMG, Single-fiber electromyography; TPMT, thiopurine methyltransferase

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37.1 Myasthenia Gravis (MG)

Key Facts

- **Definition** – MG is an autoimmune disorder caused by Ab to motor post-synaptic AChRs.
- **Epidemiology** – Incidence 1.7–21.3/million/year; prevalence 15–179/million.
- **Clinical features** – MG shows fluctuating muscle weakness that worsens with activity and improves with rest.
- **MG subtypes** – Ocular, generalized, thymoma-associated; MuSK-associated, seronegative.
- **Diagnostic markers** – Clinical features, Tensilon test
  - **Blood** – Detection of anti-AChR Ab, anti-MuSK Ab, low-affinity anti-AChR Ab, anti-LRP4 Ab in blood.
  - **Neurophysiology** – Repetitive nerve stimulation, Single-fiber electromyography.
- **Top differential diagnoses** – LEMS, congenital myasthenic syndromes, motor neuron disorders, polineuropathies, mitocondrial myopathies, botulism.
- **Principles of treatment**
  - **Symptomatic treatment** – Cholinesterase inhibitors.
  - **Immunomodulation** – PLEX, IVIG, corticosteroids, immunosuppressive drugs, and thymectomy.
- **Prognosis** – Mortality rate ~ 2 %.

Autoimmune ion channel disorders of the peripheral nervous system share the common pathogenesis of being mediated by specific antibodies against antigenic targets located at the neuromuscular junction, either pre- or post-synaptically, or on autonomic ganglia. They include myasthenia gravis, Lambert-Eaton myasthenic syndrome, acquired neuromyotonia, and autoimmune autonomic ganglionopathy. Each disease has been initially associated to one specific autoantibody, but recent research has identified new antigenic targets represented by proteins in close association to the target antigen originally described. These findings suggest that the pathogenesis of autoimmune ion channel disorders is more complex than previously thought, and new disorders or variants of the classical clinical presentations are likely to be reported in the future.

37.1.1 Definition

MG is an antibody-mediated autoimmune disease of the neuromuscular junction (NMJ) causing muscle weakness and fatigability, increased by exercise and relieved by rest, associated in about 85 % of patients with antibodies to the acetylcholine receptor (AChR), and less frequently with antibodies to other antigens of the post-synaptic membrane [1].

37.1.2 Epidemiology

Incidence rates reported for MG varied between 1.7 and 21.3/million/year, with a female ratio of 2:1 in younger adults and a reversed sex ratio in older people. Prevalence ranged from 15 to 179/million population [2].

37.1.3 Clinical Features

MG is a prototypical antibody-mediated disorder of the NMJ, characterized by fluctuating muscle weakness that worsens with activity and improves with rest. Ocular muscles weakness with drooping of the eyelid and/or diplopia is the most frequent presentation at onset. The majority of MG patients show progression to generalized MG within 2 years from the onset. Generalized MG affects facial, limb, axial, respiratory, and bulbar muscles in variable combinations. Severity of bulbar and respiratory muscles involvement may require nasogastric feeding and assisted ventilation. Typically, symptoms fluctuate during the day and may worsen after incurrent illness, infections, emotional stress, or after surgery. Long-lasting spontaneous remission is uncommon [1].

37.1.3.1 MG Subtypes

1. *Ocular MG*: weakness limited to extraocular muscles; anti-AChR antibodies are detected in up to 50 % of patients.
2. *Generalized MG*: historically divided into early onset (usually before the age of 40 years, more frequent in females with positive anti-AChR antibodies and hyperplastic thymus) and late onset (more frequent in males with normal or atrophic thymus).
3. *Thymoma-associated MG*: occurs in males and females, peak onset at the age of 50 years. The disease tends to be more severe compared with that in patients without thymoma. Symptoms persist after tumor removal.
4. *Muscle-specific receptor tyrosine kinase (MuSK)-associated MG*: predominant involvement of ocular, facial, bulbar, and neck muscles, with relative sparing of the limbs, and increased frequency of myasthenic crises (hence called "oculo-bulbar MG"); patients may show facial and tongue muscle weakness and atrophy; thymus gland is usually not involved.
5. *Seronegative MG*: includes patients lacking both anti-AChR and anti-MuSK antibodies; clinically indistinguishable from MG with anti-AChR antibodies; low-affinity antibodies to the AChR (not detected by routine immunoassays) have been reported in some seronegative patients.

37.1.3.2 Immunopathogenesis

MG is a T cell-dependent B cell-mediated disorder of the NMJ. The key factor(s) triggering the autoimmune response in MG is still unknown. The thymus is likely to play a major role; indeed, at least 80 % of MG patients with anti-AChR antibodies show thymic hyperplasia, and hyperplastic thymuses contain myoid cells expressing the AChR as well as cells and molecules required to start, or perpetuate, an autoimmune response [1]. Recently, innate immunity, the first line of defense against pathogens, has been extensively investigated in MG. The expression of some toll-like receptors is increased in epithelioid cells in MG thymuses as well as other toll-associated molecules, suggesting that a viral infection might play a role in increasing AChR expression in the thymus and lead to the synthesis of specific autoantibodies [3]. Whatever the initiating event, the clinical features of MG are the result of the autoimmune attack against different antigenic determinants of the NMJ (either the AChR or other proteins in close association with it), ultimately causing loss of functional AChRs and impairment of neuromuscular transmission.

37.1.3.3 Laboratory

Blood The following immunoreactivities have been identified [4]:

1. *Anti-AChR antibodies*: belong to the IgG1 or IgG3 subclass, able to activate complement; bind to the extracellular domain of the AChR.
2. *Anti-MuSK antibodies*: belong to IgG4 and do not activate complement; MuSK is a protein involved in the correct clustering of AChRs at the NMJ; their effect again disrupts the postsynaptic membrane.
3. *Low-affinity IgG antibodies to AChR* [5]: detected in some seronegative MG patients, bind to AChRs clustered with rapsyn on the surface of transfected cells, belong to IgG1 subclass and activate complement.
4. *Anti-LRP4 antibodies (LDL receptor-related protein 4)*: detected in some seronegative MG patients; LRP4, a crucial protein for the correct NMJ formation during development, acts as a receptor for agrin, causing MuSK activation; belong to the IgG1 subclass, able to activate complement; their pathogenic role needs further studies [6].

37.1.4 Diagnosis

Diagnosis of MG relies upon clinical, serological, and electrophysiological testing.

1. Clinical and pharmacological tests:
   - Characteristic history of painless, fluctuating muscle weakness and fatigability
   - (Edrophonium chloride) Tensilon test (2 mg i.v. under cardiac monitoring; usually followed by 8 mg after 30 s. if there is no response to the first dose)
2. Serological tests:
   - Anti-AChR antibodies are found in 80–85 % of patients with generalized MG and 50 % with ocular MG; titers do not predict the severity of the disease in each patient.
   - MuSK antibodies: should be tested in MG patients negative for Anti-AChR antibodies (particularly in patients with oculo-bulbar involvement).
   - Low-affinity Anti-AChR antibodies: detected in patients without AChR and MuSK antibodies (not commercially available) [5].
   - Anti-LRP4 antibodies: detected by means of cells transfected with full-length human LRP4 (not commercially available) in 18.7 % of patients double-negative for AChR and MuSK antibodies [6].
3. Electrophysiological tests [7]:
   - Repetitive nerve stimulation (RNS) at 2–5 Hz causes progressive reduction of the amplitude of the compound muscle action potential; if the reduction is greater than 10 %, the test is considered positive ("decremental response"). RNS is usually positive in about 75 % of patients with generalized and in 50 % with ocular MG. RNS should always be performed on proximal muscles.
   - Single-fiber electromyography (SFEMG) is the most sensitive test for MG (>95 % positive in ocular and generalized MG); however, abnormal jitter is not specific for MG, since it can be found increased in disorders such as amyotrophic lateral sclerosis, inflammatory myopathies, or Lambert-Eaton myasthenic syndrome.

Additional diagnostic investigations include contrast-enhanced chest MRI or CT scan to detect thymic enlargement or thymoma, and tests for thyroid function due to the frequent occurrence of hyper- or hypothyroidism in MG.

37.1.5 Differential Diagnosis

Differential diagnosis includes disorders of the peripheral or central nervous system (Table 37.1).

Table 37.1 Differential diagnoses of MG and LEMS

MG
LEMS: autonomic dysfunction, absent deep tendon reflexes, rare ocular involvement
Congenital myasthenic syndromes: onset in childhood, absence of autoantibodies, no effect of immunotherapy
Motor neuron disorders: fasciculations, muscle atrophy, corticospinal involvement
Proximal myopathies: CPK, EMG findings, muscle imaging and muscle biopsy
Mitocondrial myopathies: bilateral eyelid ptosis and ophthalmoplegia, no diplopia, slow course, muscle biopsy and genetic studies
Polineuropathies: EMG findings
CNS disorders with impairment of cranial nerves: acute/subacute onset, signs of brainstem involvement
Botulism: autonomic and pupillary involvement, rapidity and pattern of progression
LEMS
MG: ocular and bulbar involvement is typical of MG; absence of tendon reflexes and autonomic dysfunction suggest LEMS.
Proximal myopathies: (degenerative, inflammatory myopathies including inclusion body myositis in older patients): CK levels, dysautonomia and neurophysiological findings differentiate LEMS from these conditions.
Inflammatory polyneuropathies: LEMS does not cause sensory symptoms and signs, pain, and CSF is normal; again, neurophysiological data allow the correct diagnosis

37.1.6 Therapy

37.1.6.1 Symptomatic Treatment

Cholinesterase inhibitors inhibit the breakdown of acetylcholine (Ach) at the neuromuscular junction, thus increasing the availability of Ach to bind AChR. Pyridostigmine bromide is the most widely used compound, average doses are 30–90 mg every 4 h. A sustained release form (180 mg) of the drug is available and prescribed at bedtime to improve weakness in the morning.

37.1.6.2 Short-Term Immunomodulation

MG exacerbations can be rapidly improved by short-term immunomodulating strategies, namely plasma exchange (PLEX) or high-dose intravenous immunoglobulins (IVIG).

PLEX Rapidly reducing the amount of circulating antibodies, induces improvement within the first week of treatment. There is no agreement on the optimal protocol to be adopted; one plasma volume should be processed during each session, performed every other day; a minimum of two, up to 4–6 sessions are performed [1, 8].

More recently, semiselective techniques have been introduced in clinical practice. They use filters able to remove mainly IgG from the patient's plasma without the need for any replacement fluid. Different adsorbents are available. Filters with Protein A and anti-human IgG are particularly efficient in removing massively circulating IgG and hence pathogenic autoantibodies [9].

IVIG Are prescribed with the same indications of PLEX; the efficacy of IVIG and PLEX has been investigated in a controlled fashion, and the two options were found to be equally effective at the time point chosen for clinical assessment [10]. The standard dose regimen is of 400 mg/kg/bw/day for 5 days; two administrations of 1 g/kg vs 2 g/kg have been found to be equally effective. IVIG are usually well tolerated.

37.1.6.3 Long-Term Immunomodulation

Cholinesterase inhibitors rarely induce stable and sustained improvement.

Corticosteroids Corticosteroids (particularly prednisone) are prescribed when the clinical picture is not controlled by cholinesterase inhibitors alone [1]. Prednisone starting dose range is 0.5–1 mg/kg/bw/day. Temporary worsening of the disease can occur during the first week of corticosteroids treatment. Once optimal improvement is obtained, the ongoing dose can be switched to an alternate day regimen and then gradually tapered to the *lowest effective dose*. The occurrence of relapses or impossibility to withdraw or reach a minimal maintenance dose are indications to start the association with an immunosuppressant.

37.1.6.4 Immunosuppressive Drugs

The majority of patients need long-term maintenance of low-dose corticosteroid to avoid relapses, thus increasing the incidence of side effects. In this regard, immunosuppressive drugs have been introduced as steroid-sparing agents [1].

Azathioprine (AZA), a purine antimetabolite, remains the drug of choice, with a safe profile regarding side effects and tolerability. The onset of benefit can be very slow and take up to 12 months. Treatment is usually started at 50 mg daily and increased by 50 mg every week up to the required dose (2–3 mg/bw/day). A randomized study provided Class I evidence regarding its steroid-sparing effect [11]. Measurement of Thiopurine Methyltransferase (TPMT) activity or checking for TPMT genotype [12] status can be considered to better address the issue of potentially severe side effects.

Alternative immunosuppressive drugs include micophenolate mophetil (MMF), methotrexate (MTX), cyclosporine A (CYA), cyclophosphamide (CYP), and tacrolimus.

MMF Blocks purine synthesis in both B and T lymphocytes. The common dose is 1 g twice daily. MMF is considered a first-line drug for the treatment of MG, as suggested by observational

studies, and is currently prescribed particularly in North America.

MTX Prescription is indicated in patients who did not respond to first-line immunosuppressive drugs; the maximum dose is 20 mg/week; a recent study showed a similar steroid-sparing effect of MTX and AZA.

CYA Inhibits T cell function by disruption of calcineurin signaling and reduced production of interleukin 2. However, at the doses proposed with earlier studies (5–6 mg/kg/bw/day), side effects of hypertension and nephrotoxicity are common. CYA should therefore be considered only in patients intolerant or unresponsive to AZA or MMF.

CYP Is an alkylating agent with strong immunosuppressive activity on B cells. The effect of CYP given in monthly pulsed doses of 500 mg/m^2 with positive results. Impressive response has been also obtained after administration of 50 mg/kg IV for 4 days followed by rescue therapy with granulocyte colony-stimulating factor.

Tacrolimus Is a macrolide compound belonging to the same immunosuppressive class as CYA, with less nephrotoxicity. The doses range from 3 to 5 mg a day, or 0.1 mg/kg/day.

Rituximab Is a chimeric monoclonal antibody directed against the CD20 antigen on the surface of B cells. Small observational studies reported significant improvement in treatment-refractory MG. Sustained improvement lasted up to 1 year. Improvement has been also reported in refractory anti-MuSK-associated. MG.

37.1.6.5 Thymectomy

The absolute indication to thymectomy is the presence of thymoma. Randomized controlled studies on the effect of surgery in MG without thymoma are not available. A metanalysis of the literature on this topic concluded that thymectomy should be considered as a treatment option for patients with non-thymomatous MG to increase the probability of remission or improvement as stated after ad hoc metanalysis [13]. Thymectomy should not be performed as an emergency procedure; patients with severe forms of the disease must be stabilized with PLEX/IVIG and adequate immunosuppression before surgery. There is general agreement that non-thymomatous MG patients with generalized MG and disease onset before the age of 50 years may benefit from thymectomy. The issue of thymectomy in patients with anti-MuSK MG is still controversial.

37.1.6.6 Myasthenic Crisis

Myasthenic crisis is a severe and potentially life-threatening exacerbation of the clinical picture leading to respiratory insufficiency requiring admission to the intensive care unit (ICU) for assisted ventilation. The expert opinion is that PLEX or IVIG should be performed soon and associated with high-dose corticosteroid therapy (or the ongoing dose increased).

37.1.6.7 Drugs to Be Avoided in MG

Some drugs are contraindicated or must be used with great caution in patients with MG, particularly a restricted group of antibiotics. A list of contraindicated drugs is reported in Table 37.2.

Table 37.2 Drugs to be avoided or contraindicated in MG

Contraindicated	Penicillamine
To be used with great caution	Curare drugs
	Botolinum toxin
	Quinine, quinidine and procainamide
	Amynoglicosides
	Macrolides
	Fluoroquinolones
	Telithromycine
	Magnesium salts i.v.
	Interferon alfa
Might worsen MG	Benzodiazepines
	Beta-blockers
	Lithium salts

37.1.7 Prognosis

The prognosis of MG has not been properly investigated due to the lack of national registries, shortness of follow-up, and heterogenous definition of outcome measures. However, prior to the introduction in 1934 of anticholinesterase inhibitors, about 70 % of patients died of respiratory failure; mortality was subsequently reduced after the introduction of antibiotics, and in the fifties it was further decreased by up to 15 % after the improvement of mechanical ventilation. Later on, the use corticosteroids and immunsoppressive drugs, together with PLEX and IVIG in patients with acute worsening, dramatically changed the natural course of the disease. Mortality rate is about 2 % [14–16].

MuSK-positive MG can be more severe than AChR-positive and double-negative MG as demonstrated by the high incidence of bulbar symptoms and respiratory crises, and poor response or intolerance to acetylcholinesterase inhibitors [16, 17]. On the contrary, double-negative patients have a course similar to that of AChR-positive patients [16]. Complete stable remission (CSR), defined as no symptoms or signs of MG for at least 1 year without ongoing treatment, was recorded in 3.6 % of MuSK-positive compared with 22 % in AChR-positive and double-negative MG. In the same large series of MG patients the occurrence of CSR was associated with onset before the age of 40 years and less severe clinical stages at maximal worsening (ocular-generalized MG) [16].

A large cohort of double-seronegative MG patients has been recently reported from Europe; the frequency of LRP4 antibodies was 18.7 %; the clinical features and response to treatment seemed to be similar to that of AChR-positive MG [6]. However, further studies regarding the clinical features and outcome of the subgroup of LRP4-associated MG are needed.

37.2 Lambert-Eaton Myasthenic Syndrome (LEMS)

Key Facts

- **Definition** – *LEMS* – Autoimmune disorder caused by Abs against VGCC of the presynaptic membrane of the NMJ.
- **Epidemiology** – Incidence 0.75 per million; prevalence 3.4 per million.
- **Clinical features** – Progressive proximal muscles weakness affecting the lower limbs more than the arms; post-exercise facilitation, autonomic dysfunctions.
- **Diagnostic markers** – small CMPs; RNS with increment above 100 % at high frequency of stimulation (20–50 Hz) or after post-exercise stimulation (typical of LEMS); blood anti-VGCC detected by immunoprecipitation.
- **Top differential diagnosis** – MG, motor neuron disorders, proximal myopathies.
- **Principles of treatment** – 3.4 diaminopyridine, immunosuppressive, immunomodulatory.
- **Prognosis** – 18/23 with paraneoplastic LEMS died after a median of 8 months; 21/25 patients with non-paraneoplastic LEMS were alive after a median time of 6.9 years.

37.2.1 Definition

LEMS is an autoimmune disorder caused by specific antibodies against the voltage-gated calcium channel (VGCC) of the presynaptic membrane of the neuromuscular junction, involving mainly the proximal muscles of the four limbs [18].

37.2.2 Epidemiology

LEMS is a rare disorder, with a reported incidence of up to 0.75 per million and prevalence of 3.4 per million. The disease is associated with small cell lung cancer (SCLC) in about 60–70 % of patients (SCLC-LEMS), rarely with other tumors; paraneoplastic LEMS may coexist with cerebellar degeneration, sensory neuronopathy, or encephalomyelitis. The median age at onset of SCLC-LEMS is 60 years, more frequently in men. Non-paraneoplastic LEMS (NT-LEMS) can be seen at all ages.

37.2.3 Clinical Features

LEMS usually presents with progressive proximal muscles weakness affecting the lower limbs more than the arms; compared with MG, LEMS affects preferentially trunk and limb muscles rather than the bulbar ones. The autonomic nervous system is frequently and variably affected in the majority of LEMS patients, with orthostatic hypotension, dry mouth and eyes, hyperhidrosis, constipation, and impotence (see Chap. 36). The multivariate analysis of clinical features of LEMS in a large cohort of patients identified smoking, weight loss, Karnofski score, bulbar symptoms, and male impotence as independent predictors for an associated SCLC [19].

Physical examination shows weakness of proximal muscles and waddling gait. Deep tendon reflexes are usually decreased or absent. The phenomenon of post-exercise facilitation, a typical feature of LEMS, albeit not always present, can mask diminished reflexes that should therefore be tested after a period of rest.

37.2.4 Pathophysiology

Anti-VGCC antibodies are considered pathogenic; since the same antigen is expressed in SCLC and at the pre-synaptic membrane, a cross reaction is likely to cause the autoimmune attack leading to the typical dysfunction of the neuromuscular transmission demonstrated by neurophysiological studies.

37.2.5 Diagnosis

Clinical features Proximal muscle weakness, post-exercise facilitation (when present), reduced or absent deep tendon reflexes, and autonomic dysfunction.

Neurophysiological studies Low compound muscle action potential; RNS with a decremental response at low frequency (2–3 Hz), as observed in MG; RNS with increment above 100 % at high frequency of stimulation (20–50 Hz) or after post-exercise stimulation (typical of LEMS).

Anti-VGCC assay Anti-VGCC P/Q type are detected by immunoprecipitation. Anti-VGCC are highly specific for LEMS and are found in up to 90 % of patients.

Neoplastic screening All patients with a diagnosis of LEMS should be submitted to CT and FDG-PET, to be periodically repeated in case of normal findings.

37.2.6 Differential Diagnosis

The differential diagnosis of LEMS is reported in Table 37.1.

37.2.7 Therapy

Treatment of the underlying tumor when present (surgery, chemotherapy)

Symptomatic treatment: 3.4 diaminopyridine (3.4 DAP) (10–20 mg 3–4 times/day) improves neuromuscular transmission by blocking voltage-gated potassium channels, thus prolonging the action potential and the opening time of VGCC. The recommended starting dose is 15 mg a day. No single dose should exceed 20 mg. Amifampridine (3,4-diaminopyridine phosphate) is now available for clinical use.

Immunosuppressive treatment In case 3.4 DAP does not control satisfactorily the clinical picture, immunosuppressive treatment with

prednisone in association with azathioprine must be considered (the treatment protocol is similar to that used in MG).

Immunomodulatory treatments Treatment with IVIG or PLEX can be considered for patients with severe weakness when immunosuppression has not exerted its full effect or results obtained are inadequate. Treatment schedules are similar to those proposed for MG.

37.2.8 Prognosis

In a group of 50 patients with LEMS, 25 had carcinoma; the risk of being affected by tumors sharply lessened 2 years after the diagnosis of LEMS and reached very low levels in 4–5 years. No carcinoma was found in the remaining 25.

One patient with breast carcinoma was alive after 10 years; one was lost to follow-up. Eighteen of the remaining 23 carcinomatous patients died after a median time of 8 months (mean 10 months) from the diagnosis of the tumor; three patients had complete remission of the LEMS symptoms.

One of the 25 LEMS patients without carcinoma was lost to follow-up; three patients died from other causes 7, 3.7, and 16.7 years after the onset of LEMS. The remaining 21 patients were alive at a median of 6.9 years (mean 6.1; range 11 months – 14 yrs) after the beginning of LEMS [20].

37.3 Acquired Neuromyotonia (NMT)

37.3.1 Definition

Acquired neuromyotonia (NMT) (alias Isaac's syndrome) is a clinical syndrome of peripheral nerve hyperexcitability associated with antibodies to voltage-gated potassium channels (VGKC). Anti-VGKC antibodies have been described in association with NMT, Morvan's syndrome, limbic encephalitis, and faciobrachial dystonic seizures [20] (see Chap. 27).

37.3.2 Clinical Features

NMT is characterized by diffuse persistent fasciculations (myokimias) spreading in a wavelike fashion in the involved muscles (limbs and trunk diffusely). Patients complain of painful muscle stiffness at rest, cramps, weakness exacerbated by exercise, paresthesias, fatigability, and delayed relaxation of muscles (pseudomyotonia). Muscle hyperactivity continues during sleep. Patient's with Morvan's syndrome show also personality changes, irritability, and sleep disturbances. Some patients complain also of hyperhidrosis.

NMT has been reported in association with lung cancer, thymoma, Hodgkin lymphoma, and thyroid disorders; in a minority of patients the disease occurs in association with autoimmune myasthenia gravis.

The average age at onset is 46 years of age for men and 48 for females with a male predominance of about 2:1.

Key Facts

- **Definition** – Acquired neuromyotonia (NMT) is a syndrome of peripheral nerve hyperexcitability associated with antibodies to voltage-gated potassium channels (VGKC).
- **Epidemiology** – Prevalence: unknown; onset: 46–48 years.
- **Clinical features** – Diffuse persistent fasciculations (myokimia), muscle cramp, and hyperhidrosis.
- **Diagnostic markers** – EMG: spontaneous and repetitive discharges of single motor units, neuromyotonic discharges, afterdischarges following stimulation of motor nerves; detection Ab anti-VGKC in blood.
- **Principles of treatment** – PLEX, IVIG, prednisone, azathioprine.

37.3.3 Pathophysiology

Muscle hyperactivity is thought to be caused by loss of function of voltage-gated potassium channels located in the distal portion of motor nerves; interference with channel activity results in decreased outward potassium currents. The pathogenic role of IgG against VGKC has been demonstrated by passive transfer to mice or by in vitro studies using transfected cells.

37.3.4 Diagnostic Markers

Blood Anti-VGKC assay: potassium channel complex autoantibodies are detected in blood by immunoprecipitation of dendrotoxin-labeled VGKCs.

Antibodies against potassium channels have been found to be directed to: (a) contacting-associated protein 2 (caspr2) localized at juxtaparanodes in myelinated axons (more frequently observed in NMT or Morvan syndrome), (b) glioma-inactivated 1 protein (LGI1) strongly expressed in the hippocampus in patients with limbic encephalitis, and (c) Tag1/contactin-associated protein 2 [21]. Assay of VGKC, caspr2, and LGI1 antibodies are now available.

Neurophysiological findings EMG recordings show spontaneous and repetitive discharges of single motor units, neuromyotonic discharges, and afterdischarges following stimulation of motor nerves or after their F-waves. Neuromyotonic activity is blocked by local curare administration.

Neoplastic screening All patients with a diagnosis of NMT should be submitted to CT and total body FDG-PET.

37.3.5 Therapy

Treatment of underlying cancer may cause improvement or remission of symptoms in some patients. Immunomodulation for NMT patients includes a course of PLEX able to induce a rapid reduction of spontaneous activity as demonstrated by clinical and neurophysiological findings; IVIG can also be considered as an alternative to PLEX. No studies are available on long-term immunosuppression of NMT; some patients have been treated with the association of prednisone with azathioprine with positive results. Treatment schedules are similar to those reported for MG and LEMS.

37.4 Autoimmune Autonomic Ganglionopathy (AAG)

See also Chaps. 27 and 35.

Key Facts

- **Clinical features** – Disorder of dorsal root ganglion cells with impairment of both sympathetic and parasympathetic functions (orthostatic hypotension, intestinal and bladder dismotility, photophobia, dry eyes and mouth, anhidrosis, and erectile dysfunction).
- **Diagnosis** – Detection of anti-ganglionic AChRs Ab (POTS and CIP).
- **Differential diagnosis** – Chronic inflammatory demyelinating polyneuropathy, hereditary sensory and autonomic neuropathies.
- **Principles of treatment** – No specific treatment protocols are recommended.

37.4.1 Definition

Autoimmune autonomic ganglionopathy (AAG) is a disorder of dorsal root ganglion cells that has been recognized as an isolated neurological entity within the spectrum of immune-mediated autonomic neuropathies due to the discovery of antiganglionic AChR antibodies [22, 23]. The disease is characterized by the impairment of both sympathetic and parasympathetic functions.

37.4.2 Clinical Features

Antecedent upper respiratory or gastrointestinal tract infections have been reported in some patients. The onset of the disease can be acute or subacute, or gradual. Typical cases present with orthostatic hypotension (the most common symptom), intestinal dismotility, flaccid bladder, photophobia, dry eyes and mouth, anhidrosis, and erectile dysfunction.

Low titer of antibodies to ganglionic AChR have been reported in a minority of patients affected with the postural tachycardia syndrome (POTS) (see Chap. 36) characterized by increased heart rate without orthostatic hypotension while standing; the same observation has been reported for patients with chronic intestinal pseudo-obstruction (CIP). Therefore, both POTS and CIP may represent a restricted form of AAN [24].

37.4.3 Pathophysiology

Serum ganglionic AChR antibodies isolated from AAG patients impair neuronal AChR currents and inhibit fast cholinergic transmission in isolated ganglia.

37.4.4 Diagnostic Markers

Clinical features Particularly orthostatic hypotension and gastrointestinal symptoms, without evidence of system degeneration.

Blood Antiganglionic AChR assay: about 50 % of patients are positive for anti-α3 AChR antibodies

CSF Elevated protein may be observed in some patients

Sural nerve biopsy Shows variable reduction of unmyelinated fibers

Total body CT scan and/or FDG PET To exclude neoplasmas.

37.4.5 Differential Diagnosis

See Chap. 36.

37.4.6 Therapy

No specific treatment protocols are recommended for AAG. Experience from case reports or small patients series suggests that initial treatment with IVIG or PLEX can be beneficial [25]. Improvement is then maintained with long-term immunosuppression with prednisone slowly tapered along the clinical follow-up; among immunosuppressants, azathioprine, mycophenolate mofetil, or cyclophosphamide have been used. Slow improvement after treatment with rituximab has been also reported. It must be underlined that response to immunotherapy has been observed also in patients with seronegative putative AAG, indicating the need to treat patients with an AAG phenotype [26].

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Muscular Dystrophies

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Abbreviations

BMD, Becker muscular dystrophy; CPAP, continuous positive airway pressure; CK, creatine kinase; CPF, cough peak flow; CAPN3, calpain 3 gene; *CAV3*, caveolin 3 gene; DMD, Duchenne muscular dystrophy; DM1, myotonic dystrophy type 1; *DMPK*, myotonic dystrophy protein kinase; emg, electromyography; FKRP, fukutin-related protein gene; FSHD, facioscapulohumeral dystrophy; FVC, forced vital capacity; GCs, glucocorticoids; LGMD, limb-girdle muscular dystrophies (1, autosomal dominant; 2, autosomal recessive); NIV, noninvasive ventilation; OSA, obstructive sleep apnoea; PSG, polysomnography; RNA, ribonucleic acid; SBD, sleep breathing disorders

Muscular dystrophies are a group of inherited and degenerative disorders that commonly manifest with progressive skeletal muscle weakness and wasting, frequently complicated by respiratory failure and/or cardiac involvement.

Despite substantial progress in understanding the pathophysiological basis of these diseases, no pharmacological therapies have been identified that significantly modify the progression of these disorders. Definition of guidelines for treatment of complications of the most frequent dystrophies has improved the quality of life and survival of patients. For the less common forms, there are no sufficient data on disease natural history to define guidelines for care and treatment of disease and complications, and the prognosis remains severe.

In this chapter, we discuss the prognosis of the most frequent muscular dystrophies.

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38.1 Dystrophinopathies

Key Facts

- **Terminology and definitions** – Dystrophinopathies are inherited recessive X-linked degenerative skeletal muscle disorders caused by mutations of *DMD* dystrophin gene (locus Xp21.2).
  DMD is the most severe form (incidence 21.7 per 100,000 male live births); BMD is the milder allelic dystrophy (incidence 3.2 per 100,000)
- **Clinical features** – DMD depicts delayed motor development due to proximal lower limb weakness with tip-toe walking, lumbar hyperlordosis, scoliosis, and finally, respiratory failure. Walking ability is lost before teens. BMD shows highly variable disease severity; patients usually maintain the ability to walk and have a normal life expectancy.
- **Diagnostic markers**
  - **Blood** – Increase of muscle enzymes
  - **Genetics** – Both DMD and BMD are X-linked, recessively inherited
  - **Muscle biopsy** – Muscle fiber degeneration and necrosis, and early inflammatory changes more severe in DMD than in BMD
  - **Neurophysiology** – Myopathic emg
- **Top differential diagnoses** – Polymyositis, congenital and metabolic myopathies
- **Prognosis**
  - **Treatment** Symptomatic and supportive
  - **Disability** – DMD: loss of autonomous walking at 12–15 years of age; life expectancy 19–25 years. BMD: highly variable (loss of walking at 30–40 years, or retained ability to walk often with normal life expectancy)

38.1.1 Definition

The term dystrophinopathies refers to a group of muscular dystrophies due to mutations (mainly deletions) in the huge *DMD* gene (locus Xp21.2), encoding for dystrophin. This 427-kilodalton protein is expressed in skeletal and cardiac muscles, along with smooth muscle fibers, cortical, Purkinje, Schwann, glial, retinal, and kidney cells. Along with α–β–γ and δ-sarcoglycan, dystrophin forms the dystrophin–glycoprotein complex, anchoring the sarcomere to the extracellular matrix. Dystrophinopathies include the most severe form, Duchenne muscular dystrophy (DMD), and the milder allelic, Becker muscular dystrophy (BMD).

Mutations disrupting the reading frame create a truncated RNA, which is rapidly degraded, causing the absence of dystrophin in DMD. Mutations maintaining the reading frame lead to a partially functioning protein, patchily distributed on muscle fibers, causing BMD.

38.1.2 Epidemiology

The incidence of DMD in Italy was estimated to be 21.7 per 100,000 male live births and that of BMD of 3.2 per 100,000 [1], similar to the data reported in other studies on European populations.

38.1.3 Clinical Features

DMD patients may present a mild delay of motor development, and most of them never achieve the ability to jump or run, because of proximal lower limb muscular weakness. Diagnosis usually occurs at 4–5 years of age. Muscular strength progressively deteriorates, and patients lose the ability to walk before their teens. A few patients, with residual partially functioning dystrophin, lose the ability to walk at around 15 years (intermediate muscular dystrophy).

Besides muscular weakness, the disease is characterized by early and progressive Achille tendon retractions, causing a tip-toe walking and increased lumbar hyperlordosis, and scoliosis. As children grow, the scoliosis may become very severe and limit functional activities and pulmonary expansion. The progressive weakness of respiratory muscles exposes patients to recurrent chest infections, sleep-disordered breathing, and ultimately respiratory failure. In

DMD and BMD, myocardial contraction is reduced by fibrosis, which results in dilated cardiomyopathy with decreased systolic function and cardiac failure [2].

Though there is no definite therapy for this disease, the quality of life and life expectancy of patients may be improved by supportive treatments and multidisciplinary approach.

Blood Massive increase of creatine kinase (CK) values and other muscle enzymes are typical of dystrophinopathies, and particularly of DMD, in which CK may be 10–20 times greater than normal values. In BMD, particularly in children, CK values may be as high as in DMD; in adult BMD patients, CK is usually 3–5 times greater than normal values.

Muscle biopsy Reveals some pathognomonic findings in DMD, such as increased endomysial connective tissue, fiber size variability, central nuclei, muscle fiber degeneration, and necrosis; inflammatory changes may be seen early in the course of the disease. In BMD children, muscle biopsy findings may be similar, though less severe; in adult BMD patients, minor changes such as central nuclei and fiber size variability are usually observed. Immunochemical investigations and Western blot analysis show the absence of dystrophin in DMD and reduced protein expression in BMD.

Genetics DMD and BMD are recessively X-linked inherited; molecular analysis of dystrophin gene may show large deletions and duplications, or small rearrangements, including nonsense mutations.

38.1.4 Therapy

TREAT-NMD, which provides an infrastructure to ensure that the most promising new therapies, has developed brief standards of care for DMD, which are available on the TREAT-NMD Web site (www.treat-nmd.eu).

Due to the complexity of the disease, a multidisciplinary approach is necessary. During follow-up, functional activities and muscle strength should be monitored by appropriate, validated, and reliable outcome measures [3]. Orthopedic orthesis, such as night splints, are recommended in ambulant children to counteract loss of dorsiflexion at the ankle; when ankle retractions become severe and impact negatively on posture and walking, surgical tenotomies may become necessary, followed by ankle–foot orthesis. When children are near to losing the ability to walk, knee–ankle–foot orthesis should be proposed to prolong ambulation. A surgical approach is suggested for severe progressive spine deformity with a Cobb angle greater than 25–30°.

In the presence of dilated cardiomyopathy, inhibition of the renin–angiotensin–aldosterone system, either alone or combined with beta-blockade, can delay progressive left ventricular dysfunction [4]. Early initiation of treatment with perindopril is associated with a lower mortality [5].

DMD/BMD carriers should also have cardiac investigation (echocardiogram and ECG) at least every 5 years or more frequently if abnormalities are found.

38.1.5 Prognosis

Cardiomyopathy is a common cause of morbidity and death in patients with Duchenne muscular dystrophy. In a cross-sectional analysis of clinical data regarding 340 DMD patients [6], the prevalence of cardiomyopathy (defined as shortening fraction (SF) < 28 % or ejection fraction (EF) <55 %) was 27 % and was significantly associated with age and clinical stage. Cardiac involvement increased from 5 % of DMD aged 0–5 years to 38 % of patients aged 14–17 years and 61 % of patients aged 18 years or older. There was significantly increased prevalence of cardiomyopathy in the late nonambulatory stage and a trend toward increased presence of cardiomyopathy in the early nonambulatory stage [4, 6].

After the loss of autonomous walking, which in DMD occurs between 12 and 15 years of age, muscular strength continues to deteriorate. The life expectancy in DMD averages between 19 and 25 years and is limited by cardiorespiratory complications.

Disease severity and progression in BMD patients is highly variable, depending on the type and quantity of muscle dystrophin. In classical forms, the disease is progressive, and a few patients are confined to a wheelchair at 30–40 years. In less severe forms, weakness is very mild and slowly progressive. These patients usually maintain the ability to walk and have normal life expectancy. Up to 100 % of BMD patients develop subclinical or clinical cardiac involvement, usually in the third decade of life, rarely in the first decade. One-third of patients develop dilative cardiomyopathy and/or arrhythmia with concomitant heart failure, sometimes leading to death. There is no correlation with the severity of myopathy [7].

Therefore, in both DMD and BMD, it is necessary to improve patient survival by performing strict cardiac function monitoring:

- Echocardiogram and ECG at diagnosis, every 2 years until 10 years of age, and then annually
- Annual Holter ECG, for abnormalities of cardiac rhythm

Cardiac magnetic resonance imaging may be performed to detect structural changes in the myocardium well before the onset of systolic dysfunction or overt cardiomyopathy.

Respiratory function decline represents a further negative prognostic factor in DMD patients and in wheelchair-bound BMD patients. The forced vital capacity (FVC) is the most informative parameter to follow disease progression in DMD. Once FVC begins to decline, children become more susceptible to chest infections and should be offered flu, pneumococcal, and pertussis vaccination.

In older nonambulant patients, a cough peak flow (CPF) [8] of less than 270 L/min has been associated with a high risk for pneumonia and respiratory failure and a requirement for intubation during intercurrent respiratory tract infections. An effective cough is also essential for the successful long-term use of noninvasive mechanical ventilation [9]. When coughing is ineffective, a cough-assist machine should be provided. Glossopharyngeal breathing (a volume recruitment technique) may be useful. At this stage of disease, nocturnal oxycapnography/polysomnography should be frequently monitored in older DMD patients, and particular attention is due to symptoms of nocturnal hypoventilation, such as headache and fatigue at rising and poor restorative sleep. When these symptoms are present, a noninvasive ventilation (NIV) can prolong life.

Glucocorticoids (Gcs), introduced in clinical practice about 20 years ago, are now the only pharmacological treatment. They are recommended in the international standards of care guideline for DMD, because they prolong ambulation for a mean of 2 years, reduce development of scoliosis, and delay respiratory insufficiency, therefore improving disease prognosis [10].

38.2 Limb-Girdle and Facioscapulohumeral Muscular Dystrophies

Key Facts

- **Terminology and definitions** – LGMD (Erb's dystrophy) is an autosomal dominant (LGMD1) or recessive (LGMD2) heterogeneous group of slowly progressive diseases characterized by girdle and proximal limb involvement
- **Clinical features** – LGMD and FSHD are slowly progressing diseases
  - **LGMD**: Girdle and proximal limb weakness, and atrophy, sparing of facial and extraocular muscles; onset between infancy and adult life; LGMD1 prevalence is ~2.27/100,000
  - **FSHD** wasting and weakness of facial, shoulder girdle, distal lower limb muscles; prevalence 1:14,000–20,000
- **Diagnostic markers**
  - **Blood** – Very high CK levels (LGMD), mildly elevated CK (FSHD)
  - **Muscle biopsy** – Myopathic features; immunohistochemistry/blotting with specific protein defects in different forms
  - **Genetics** – Autosomal dominant (LGMD1, FSHD) or recessive (LGMD2)
    Mutations of: *CAPN3* gene (LGMD2A), *FKRP* gene (LGMD2I); most FSHD families have reduced D4Z4 units number in EcoRI fragment on chromosome 4
  - **Neurophysiology:** Myopathic features (LGMD, FSHD)
- **Top differential diagnoses** – Congenital myopathies, other muscle dystrophies, ALS (LGMD, FSHD)
- **Principles of treatment** – Supportive
- **Prognosis**—Different subtypes may have different severity (Table 38.1); LGMD2C-F, LGMD2I, and LGMD2J presenting in early life may lead to loss of ambulation; mutations in caveolin 3 gene (CAV3) have a better prognosis. A few patients lose ability to walk, quite good prognosis quoad vitam (FSHD).

38.2.1 Limb-Girdle Muscular Dystrophies

38.2.1.1 Definition

Limb-girdle muscular dystrophies (LGMD) were initially defined on the basis of dystrophic features at muscle biopsy and predominant progressive proximal muscle involvement. Despite the definition of limb-girdle involvement, LGMD are characterized by considerable clinical heterogeneity and present clinical overlap with other muscle diseases. Onset varies between birth and late adult age.

Classification To date, at least 31 LGMD are known and classified into two main groups according to inheritance patterns, namely

1. LGMD1 for autosomal dominant subtypes
2. LGMD2 for autosomal recessive forms

38.2.1.2 Epidemiology

Overall frequency of LGMD is low, with a prevalence of 2.27/100,000 in northern England, and single entities are quite rare [11]. LGMD2A due to mutations in calpain 3 gene (*CAPN3*) is the most frequent limb-girdle dystrophy in many populations, while LGMD2I, determined by mutations in fukutin-related protein gene (*FKRP*), is the most common form in northern Europe [12].

38.2.1.3 Clinical Features

LGMD diagnosis requires clinical data, muscle biopsy, and finally, genetic testing. LGMD phenotype is generally characterized by predominant limb-girlde muscle involvement, with sparing of facial and extraocular muscles, while distal weakness may be detected later in the disease course or in severe cases.

Blood CK level could be informative, being highly increased (more than five times the normal value) in autosomal recessive LGMDs, while it is usually normal or mildly elevated in autosomal dominant forms.

Muscle biopsy Still represents an important tool in the diagnostic process. In particular, immunohistochemistry or immunoblotting for specific muscle proteins causing different LGMD forms may suggest a specific LGMD subtype and guide the genetic analysis.

38.2.1.4 Treatment

There are no established specific drug treatments for LGMD.

Rehabilitation, periodic cardiac and respiratory evaluation, and appropriate management of cardiac and respiratory complications are strongly recommended to improve LGMD quality of life and longevity.

38.2.1.5 Prognosis

LGMD prognosis has been poorly investigated due to the lack of studies on large cohorts of patients. In addition, most of the studies were retrospective; hence, only partial data on LGMD natural history are available. However, correct characterization of LGMD is important, because different subtypes may have different severity (see Table 38.1).

Table 38.1

Disease	Gene	Typical onset	Progression	Heart involvement	Respiratory involvement
LGMD1A	*TTID*	Adulthood	Slow	Rare	Rare
LGMD1B	*LMNA*	Variable	Slow	Frequent	Possible
LGMD1C	*CAV3*	Childhood	Slow	Possible	No
LGMD1D	*DNAJB6*	Adulthood	Slow	No	No
LGMD1E	*DES*	Adulthood	Slow	Frequent	No
LGMD1F	*TNPO3*	Variable	Variable	No	Possible
LGMD1G	*HNRPDL*	Variable	Slow	No	No
LGMD1H	not known	Variable	Slow	No	No
LGMD2A	*CAPN3*	Adolescence	Variable	No	No
LGMD2B	*DYSF*	Young adulthood	Variable	No	Possible
LGMD2C	*SGCG*	Childhood	Severe	Frequent	Frequent
LGMD2D	*SGCA*	Childhood	Severe	Frequent	Frequent
LGMD2E	*SGCB*	Childhood	Severe	Frequent	Frequent
LGMD2F	*SGCD*	Childhood	Severe	Rare	Frequent
LGMD2G	*TCAP*	Adolescence	Slow	Possible	No
LGMD2H	*TRIM32*	Young adulthood	Slow	No	No
LGMD2I	*FKRP*	Childhood	Severe	Frequent	Frequent
LGMD2J	*TTN*	Young adulthood	Severe	No	No
LGMD2K	*POMT1*	Childhood	Slow	No	Possible
LGMD2L	*ANO5*	Variable	Slow	No	No
LGMD2M	*FKTN*	Childhood	Moderate	Possible	Possible
LGMD2N	*POMT2*	Childhood	Slow	Rare	No
LGMD2O	*POMGnT1*	Childhood	Moderate	No	No
LGMD2P	*DAG1*	Childhood	Slow	No	No
LGMD2Q	*PLEC1*	Childhood	Slow	No	No
LGMD2R	*DES*	Young adulthood		Possible	No
LGMD2S	*TRAPPC11*	Young adulthood	Slow	No	No
LGMD2T	*GMPPB*	Childhood		Possible	No
LGMD2U	*ISPD*	Variable	Variable	Possible	Possible
LGMD2V	*GAA*	Variable	Variable	Possible	Frequent
LGMD2W	*LIMS2*	Childhood		Possible	No

To summarize, LGMD prognosis could be generally assessed by skeletal muscular progression to severe motor function disability, heart involvement, and respiratory problems. Bulbar involvement and its complications, such as the need for nasogastric feeding or gastrostomy, are uncommon.

Severe progression of skeletal muscle weakness, presenting in early life, and sometimes leading to loss of ambulation, has been mainly reported in sarcoglycanopathies (LGMD2C-F), LGMD2I, and LGMD2J. However, patients affected by other LGMD subtypes may lose walking ability, though less frequently and later in the disease course.

Patients with mutations in caveolin 3 gene (*CAV3*) seem to have a relatively better prognosis compared to patients with other mutated genes. Among these patients, only 60 % usually develop muscle weakness, while the remaining patients present myalgia, myoglobinuria, or muscle rippling. A similar behavior has been reported for LGMD2L, due to anoctamin 5 gene (*ANO5*) mutations.

Respiratory involvement has been mainly reported in sarcoglycanopathies and in LGMD2I, sometimes with respiratory failure, while the patient is still ambulant.

Heart involvement, most frequently cardiomyopathy, has been observed in particular in LGMD1B, LGMD1E, sarcoglycanopathies, and LGMD2I. However, in addition to dilated cardiomyopathy sometimes requiring heart transplant, LGMD1B shows a high incidence of arrhythmias preceding skeletal muscle involvement in some patients and often needing a pacemaker or implantable cardioverter defibrillator. A high intrafamilial phenotype heterogeneity in LGMD1B has been described, with asymptomatic members affected only by heart disease [13].

38.2.2 FacioscapulohHumeral Dystrophy (FSHD)

38.2.2.1 Definition

Facioscapulohumeral dystrophy (FSHD) is an autosomal dominant myopathy, which involves facial, shoulder girdle, and distal lower limb muscles.

38.2.2.2 Epidemiology

FSHD is a relatively common myophathy (the third common muscular dystrophy after Duchenne muscular dystrophy and myotonic dystrophy), with an estimated prevalence ranging from 1:14,000 to 1:20,000 [14].

38.2.2.3 Clinical Features

The disease is characterized by wasting and weakness of facial muscles (particularly of orbicularis oculi with difficulty in closing eyes and orbicularis oris with inability to protrude lips, to use a straw, and to whistle), shoulder girdle (scapulae winging with inability to fully abduct and/or flex arms above 45–90°), and distal lower limb muscles (weakness of foot dorsiflexors, with foot drop during walking). Clinical phenotype is very broad, ranging from isolated facial weakness to severe shoulder girdle and distal weakness. Moreover, phenotype may be extremely variable in the same family also, suggesting that other factors, such as epigenetic modifiers, may modulate genetic abnormality and phenotype.

38.2.2.4 Diagnostic Markers

Blood Mildly elevated CK

EMG Myogenic potentials, particularly in shoulder, proximal upper limb, and distal lower limb muscles.

Molecular analysis reveals in most families a reduced number of 3.3 kb units (D4Z4 units) in a polymorphic EcoRI fragment on chromosome 4, below a threshold of 38 kb [15].

38.2.2.5 Therapy

Weakness of the thoracoscapular muscles allows the scapula to lift off the chest wall during shoulder movements. Scapula stability may be achieved by specific surgical intervention. Though small case series suggest that surgical operations might produce significant benefits in selected patients, no large series have been investigated.

Strength training associated with albuterol (beta-2-adrenergic agonist, which increases muscle strength and mass in normal subjects) has

been proposed in FSHD patients, with a limited positive effect on muscle strength and volume [16].

38.2.2.6 Prognosis

The disease is usually slowly progressive, with few patients losing ability to walk. A 10-year prospective study recently reported [17] documented the natural history of 16 patients with moderately advanced FSHD: half of the patients showed a functional decline of the arms, all patients maintained useful hand function, three-quarters of patients suffered functional decline of the legs, and all patients remained ambulant.

In two previous prospective FSHD studies, patients at various stages of disease were monitored over periods of 10 and 3 years, respectively. These studies showed a clinical deterioration of patient subpopulations, not associated with patient age at disease onset, patient age, gender, or duration of disease [18, 19].

FSHD is not generally associated with cardiac or respiratory involvement; therefore, the disease prognosis quoad vitam is quite good.

38.3 Myotonic Dystrophies

Key Facts

- **Terminology and definitions**
  - DM1 (alias Steinert myotonic dystrophy) is an AD multisystemic disorders due to a trinucleotide CTG repeat of *DMPK* gene on 19q13.3. DM1 mutation frequency: 1/2760. DM2 mutation frequency: 1/1830.
  - DM2: AD due to CCTG repeat on 3q13.3-q24.
- **Clinical features** – Muscle weakness and wasting, myotonia, cataract, cardiac conduction abnormalities, endocrine changes (DM1). Onset after age 30. Myotonia is less severe in DM2 than in DM1, with mild proximal weakness over the age of 50 (DM2).
- **Diagnostic markers**
  - **Blood** – Normal or mildly elevated CK (DM1 and DM2)
  - Muscle biopsy – Type 2 fiber atrophy (DM1). Scattered thin, angular Type 2b fibers (DM2)
  - Genetics – AD (both DM1 and DM2); more than 50 to several thousand CTG repeats (DM1). Expanded allele sizes 75–11,000 CCTG repeats (DM2)
  - Neurophysiology – Myotonic discharges at emg (DM1 and DM2)
- **Top differential diagnoses** – Nondystrophic myotonias caused by mutations in genes coding for voltage-gated ion channels.
- **Principles of treatment** – Supportive
- **Prognosis:** Different DM1 subtypes have different severity. Mortality from respiratory failure is high in congenital DM1. Adult DM1 patients die at a mean age of 53.2 years (20 %), between 50 and 65 (63 %), and after 65 years of age (12 %).
  DM2 is generally milder and with older age of onset than DM1; respiratory failure may occur; left ventricular dysfunction and cardiac arrhythmias are frequent in both DM1 and DM2; muscle weakness progression is reduced and less severe in DM2 than in DM1.

38.3.1 Definition

Myotonic dystrophy type 1 (DM1), better known as Steinert myotonic dystrophy, is an autosomal dominant disorder caused by an expanded CTG repeat in the myotonic dystrophy protein kinase (*DMPK*) gene on the long arm of chromosome 19. The pathogenetic mechanism by which repeats lead to clinical signs is not completely understood; however, nuclear accumulation of ribonucleic acid (RNA) from the expanded allele induces a toxic effect on RNA processing.

38.3.2 Epidemiology

Myotonic dystrophy type 1 is the most common inherited muscular dystrophy in adults, with an estimated prevalence of 1/8000 and a mutation frequency of 1/2760 in the general population [20].

38.3.3 Clinical Features

DM1 may present different forms with congenital to adult onset.

Congenital DM1, characterized by extreme muscle weakness and mental retardation, is the most severe variant and is typically seen in sons of affected mothers.

Clinical phenotype of the adult-onset form is characterized by the myotonic phenomenon, that is, a delay in relaxation of muscle after contraction, usually present in tongue, forearm, and hand. Besides this symptom, patients usually present a typical long face, with eye ptosis and weakness of eyelid closure; masseter, temporal, and sternocleidomastoids atrophy; swallowing and speech impairment; tibial and peroneal muscles weakness with inability to extend foot and stepping walking.

The disease is multisystemic and may also involve eye lens (cataract) in young adulthood, peripheral insulin receptors with hyperglycemia; other endocrine glands can be involved with hypothyroidism, hypogonadism, and infertility. Cardiac rhythm abnormalities and respiratory failure are very frequent and represent the main cause of death.

Blood CK: normal or slightly elevated

EMG Myotonic discharges

Muscle biopsy Many fibers present multiple central nuclei, type 2 fiber atrophy.

Genetics Normal individuals have 5–37 CTG repeats, whereas patients have from more than 50 to several thousand CTG repeats in peripheral leukocytes. Repeats are usually classified in three classes of expansion: class E1 (usually includes slightly symptomatic patients), class E2 (typical disease symptoms), and class E3 (includes most congenital and infantile cases). There is no strict correlation between the class of expansion and clinical phenotype.

38.3.4 Prognosis

Congenital DM1 shows distinct clinical features that present before birth as polyhydramnios and reduced fetal movements. At birth, the main features are severe generalized weakness, hypotonia, respiratory involvement, and facial weakness with weak cry and inability to suck. Mortality from respiratory failure is high. Surviving infants experience gradual improvement in motor function, can swallow, and independently ventilate. Almost all congenital DM1 children are able to walk. Cognitive and motor milestones are delayed, and learning difficulties are typical.

Furthermore, the main problems in childhood-onset DM, with an onset age under 10 years, are developmental disorders or learning disabilities, rather than muscle symptoms.

In a 10-year study of mortality in a cohort of 367 DM1 patients, 20 % died at a mean age of 53.2 years; of these, 43 % died of respiratory failure, 20 % of cardiovascular disease, including sudden death because of arrhythmia, and 11 % of neoplasia. The mean age of death was higher for patients with early-onset disease and proximal weakness, compared with patients with distal weakness or without muscle involvement [21].

Of 180 patients with adult-type myotonic dystrophy (age at onset 10–50 years), the majority (63 %) died between 50 and 65 years of age; only 12 % died after 65 years, suggesting that survival was markedly reduced in patients compared with general populations. Pneumonia and cardiac arrhythmias were the most frequent primary causes of death and represent the most common secondary cause of death [22].

In a large cohort of 245 DM1 patients, cardiac arrhythmias were observed in 63 patients, 40 of whom required a device implant [23]. The risk of developing arrhythmias was significantly higher in men than in women and was further increased by age and severity of muscle involvement. However, all of these variables were weak predictors of arrhythmic risk, suggesting that other factors may be involved in the development of cardiac conduction abnormalities in DM1. While cardiac conduction abnormalities are a well-known complication of DM1, few studies have been conducted on primary structural myocardial involvement. In a study by Dhand and colleagues, among 27 patients, echocardiogram was abnormal in 10 patients. Abnormalities included reduced left ventricular ejection fraction, diastolic dysfunction, left atrial dilation, left ventricular hypertrophy, and apical hypokinesia [24].

Altogether, these data suggest that an annual cardiac function assessment by ECG, Holter ECG, and echocardiogram is mandatory in the follow-up of DM1 patients.

Sleep breathing disorders (SBD) and peripheral and central obstructive sleep apnoea (OSA) are present in a high proportion of DM1 patients, despite the absence of typical clinical signs and independently of diurnal respiratory involvement, often requiring noninvasive nocturnal ventilation treatment, either with continuous positive airway pressure (CPAP) or bilevel pressure support [25]. As for cardiac involvement, OSA and respiratory involvement cannot be predicted on the basis of neurological features or diurnal functional respiratory tests. Therefore, in the absence of reliable predictors, periodical evaluation by polysomnography (or at least an ambulatory cardiorespiratory monitoring) should be mandatory in these patients to ascertain, and treat if necessary, the presence of OSA or other SBD.

38.4 Myotonic Dystrophy Type 2

38.4.1 Definition

Myotonic dystrophy type 2 (DM2) is an autosomal dominant disorder, caused by an expansion of CCTG repeat on chromosome 3 (3q13.3-q24), in the region encoding the ZNF9 gene.

38.4.2 Epidemiology

Overall, the DM2 mutation frequency is rarer than DM1, and it has been estimated to be 1 in 1830 in the general population [20].

38.4.3 Clinical Features

Symptoms of the disease are myotonia usually less severe than in DM1 and frequently present only between the third and fourth decade of life, and later onset of mild proximal weakness, at fifth to seventh decade. The severity of this disease is quite variable.

Blood CK is normal or slightly increased

EMG Typical myotonic discharges

Muscle biopsy – Shows few myopathic changes, including increased fiber size variation and internalized nuclei, but the characteristic finding is the presence of scattered thin, angular, atrophic type 2b fibers

Genetics Expanded allele sizes ranging from 75 to approximately 11,000 CCTG repeats, with a mean of approximately 5000 repeats

38.4.4 Prognosis

The disease is generally milder and has an older age at onset than DM1. Also in DM2, cardiac arrhythmia and respiratory failure may occur, but are less frequent and less severe than in DM1. In a prospective study on 104 DM2 patients, over an average of 7.4 years, 6 % of patients required a pacemaker or pacer/defibrillator implantation. Three of the four deaths that occurred during the study were cardiac deaths [26].

38.5 Congenital Myopathies (CM) (See Table 38.2)

38.5.1 Definition and Clinical Features

Congenital myopathies are a group of genetic muscular disorders usually characterized by slowly progressing hypotonia and weakness since birth. Their classification is based on morphological findings at muscle biopsy. The most frequent abnormalities are rods, cores, central nuclei, and fiber-type disproportion.

38.5.2 Genetic

Many congenital myopathies are caused by different genes (e.g., nemaline myopathy is due to eight different genes). Different mutations of a single

Table 38.2 Most frequent forms of congenital myopathy, classified according to histopathological features

Disease	Inheritance	Gene	Protein	Most frequent clinical features
Nemaline rod myopathy	AD/AR	*ACTA1*	Actin, alpha skeletal	Severe neonatal onset with respiratory and feeling support[a]
	AR	*NEB*	Nebulin	Congenital, with bulbar weakness; phenotype with distal weakness[a]
	AR or AD	*TPM3*	Tropomyosin 3	Lower limb weakness
	AD	*TPM2*	Tropomyosin 2	Mild involvement; slowly progressive weakness
	AR	*TNNT1*	Slow skeletal muscle troponin	Described in Amish; severe early onset weakness, death in infancy
	AR	*CFL2*	Tropomyosin-binding protein	Rare; severe neonatal onset, respiratory distress, and death
	AD	*KBTBD13*	BTB/Kelch family member	Slowly progressive muscle weakness and typical slowness of movements
Core myopathy	AD	*RYR1*	Ryanodine receptor 1	Infantile onset, skeletal deformities, static or slowly progressive, walking delay
	AR	*RYR1*	Ryanodine receptor 1	Neonatal onset, bulbar and respiratory involvement, walking delay
	AR	*SEPN1*	Selenoprotein 1	Axial myopathy, spinal rigidity, and prominent respiratory involvement. The majority maintain independent ambulation
Centronuclear myopathy	X-linked	*MTM1*	Myotubularin	Neonatal onset, very severe muscle and bulbar weakness, external ophthalmoplegia. Early mortality
	AD	*DNM2*	Dynamin 2	Early severe onset or mild onset in late childhood or adulthood. Facial and extraocular muscle weakness, muscle limb weakness
	AR	*BIN2*	Amphiphysin	Facial weakness, ptosis, external ophthalmoplegia, masticatory weakness, proximal muscle weakness
	AR	*RYR1*	Ryanodine receptor 1	Early hypotonia and weakness, extraocular muscle impairment followed by clinical improvement

[a]Most frequent forms

gene may cause different congenital myopathies (e.g., mutations in *SEPN1* gene may produce multiminicore myopathy or congenital fiber-type disproportion or rigid spine syndrome) (Table 38.2).

38.5.3 Prognosis

In the long term, the most frequent symptoms of CM observed in the pediatric population are due to bulbar and respiratory involvement, quite often causing death in patients with early severe onset diseases. Tightness of the Achilles tendon, congenital hip dysplasia, congenital talipes equinovarus, and scoliosis, present in 40 % of patients, are further complications often beginning between birth and 16 years.

Genotype–phenotype correlations:

1. Severe neonatal onset of bulbar and respiratory deficits are observed in almost all patients with mutations in *MTM1* gene and with *ACTA1* mutation.
2. In a large pediatric cohort, no death was registered in patients with RYR1, SEPN1, and NEB mutations. Eight of 15 deceased patients were affected by NM, 7 by CNM. MTM1, ACTA1, and KLHL40. RYR1 was the most frequently identified and did not require respiratory support [27].

Less severely affected patients survive until adulthood and usually present slow progression of muscle weakness, with worsening difficulty in walking, and frequent respiratory distress [28].

Adult-onset congenital myopathies are often characterized by good prognosis.

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Inflammatory Myopathies

39

Lucia Morandi

Key Facts

- **Terminology and definitions** – Subacute-chronic inflammatory myopathies are a group of acquired disorders, sharing an autoimmune pathogenesis.
- **Clinical features** – IIMs are characterized by proximal limb muscle weakness (PM), with skin changes (DM). Early atrophy and weakness of quadriceps and finger flexors of hands with dysphagia are typical of IBM.
- **Diagnostic markers**
  - **Blood** – Elevated CK and transaminases levels; MSAs and MAAs Ab; anti-ARS, anti-SRP, and anti- Ro52 Ab.
  - **Muscle biopsy** – Is the first choice examination. It is characterized by inflammatory features, cells necrosis (PM, DM, sporadic IBM); rimmed vacuoles (IBM); HLA I positive, necrotic fibres, surrounded by sparse mononuclear cell in NAM.
  - **MRI** – May suggest muscle inflammation and help to focus the site of muscle biopsy.
  - **EMG** – Shows spontaneous activity at rest and small amplitude short duration motor units.
- **Top differential diagnoses** – Muscular dystrophies
- **Prognosis**
  - **Principles of treatment** – Steroids and immunosuppressants (PM and DM)
  - **Disability** – Survival rate of PM patients range from 77 % to 92–95 % at 5 and 10 years. No significant differences are observed between PM and DM in the course of the disease, need for continuous therapy, mortality, and quality of life. In DM the main cause of death is cancer. Most patients need support to walk within 5 years after onset of IBM, and are wheelchair-bound after 10 years.

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Abbreviations

Ab, antibodies; ARS, aminoacyl-tRNA-synthetase; CADM, clinically amyopathic dermatomyositis; CK, creatine kinase; EMG, electromyography; DM, dermatomyositis; HMGCR, 3-hydroxy-3-methylglutaryl co-enzyma A reductase; (s) and (h) IBM, (sporadic) and (hereditary) inclusion body myositis; IIM, Idiopathic inflammatory myopathy; ILD, interstitial lung disease; JDM, Juvenile dermatomyositis; MAAs, myositis associated antibodies; MRI, magnetic resonance imaging; MSAs, myositis specific antibodies; NAM, necrotizing autoimmune myositis; PM, polymyositis; Ro52, Ro ribonucleoprotein; SRP, Signal Recognition Particles;

39.1 Classification

Idiopathic inflammatory myopathies (IIMs) are a group of acquired chronic, subacute, or acute disorders, sharing an autoimmune pathogenesis.

They are currently subdivided into: polymyositis (PM), dermatomyositis (DM), sporadic inclusion body myositis (sIBM), and necrotizing autoimmune myositis (NAM). PM and DM may present during childhood (juvenile PM or DM) or may be associated with malignancy or connective tissue disorders; the latter syndromes are classified as overlap syndromes.

PM and sIBM are mediated by cytotoxic T cells, and DM by a complement-mediated microangiopathy. NAM is due to macrophages recruited by an antibody-dependent cell-mediated cytotoxicity process [1, 2].

Autoantibodies found in the sera of patients with IIMs are main tools for the diagnosis of autoimmune myopathy and contribute to the definition of disease subset. These antibodies (Ab) are divided into myositis associated antibodies (MAAs) and myositis specific antibodies (MSAs). MAAs may be present in different autoimmune connective tissue diseases with or without muscle involvement (myositis overlap syndrome). MSAs are highly selective antibodies associated with distinctive myositis subsets, such as PM and DM [3].

Some authors consider the above classification inadequate because: (1) several immune myopathies have little or no inflammation, (2) some immune myopathies with MSAs include both PM and DM patients, (3) the term polymyositis is often used to denote inflammatory myositis which are not dermatomyositis or sIBM. Accordingly, they classify IIMs according to muscle fibre pathology, immune characteristics, and the tissues involved. Their myopathological classification includes immune myopathies with perimysial pathology, myovasculopathies, immune myopathies with endomysial pathology, histiocytic inflammatory myopathy, and inflammatory myopathies with vacuoles, aggregates and mitochondrial pathology [4, 5].

39.2 Polymyositis (PM)

39.2.1 Definition

PM is a subacute or chronic myopathy characterized by proximal limb muscle weakness. The disease is due to cytotoxicity mediated by CD8+ T cells invading muscle fibres that express MHC-I antigen.

39.2.2 Epidemiology

PM is a rare disease and is considered the least common among IIMs, with an incidence of around 4 cases/million population/year. Patients with PM have higher risk for cancer (6.2 %) if compared to general population [6]. Cancer may precede, accompany, or follow the onset of polymyositis. Ovarian cancer is the most frequently associated in Europe and North America; gastric, nasopharyngeal carcinoma, and breast cancers are the most often associated in Asia. Therefore screening for cancer is highly recommended in PM patients [7].

39.2.3 Clinical Features

Subacute, symmetric, proximal limb weakness with difficulty in raising arms, walking, and climbing stairs are usually the presenting symptoms. Distal muscles may be involved in later stages of the disease, facial muscles being spared.

Arthralgia, cardiac manifestations (arrhythmia, congestive failure), probably secondary to autoimmune myocarditis, and respiratory muscle involvement may ensue over the course of the disease. Interstitial lung disease may be observed, particularly in patients with serum anti Jo-1 antibodies.

Blood Serum muscle enzymes (CK and transaminases) are usually very high at the beginning of the disease and are strongly correlated to each other.

Serum autoantibodies are a diagnostic tool for the diagnosis and the definition of the disease subset. The most frequent MSAs antibodies observed in polymyositis are Ab anti-aminoacyl-tRNA-synthetase (anti ARS), overall found in 25–35 % of PM patients. Among these, anti-Jo-1 is the most common in PM (20–30 %), while other anti ARS autoantibodies are much less frequent (no more than 5 %). Anti-signal recognition particles (SRP) antibodies and cytoplasmic proteins involved in the recognition and targeting of signals to the endoplasmic reticulum, are described in 4–6 % of adult PM patients. Among MAAs, antibody against the cytoplasmic Ro ribonucleoprotein (Ro52) is found in more than 30 % of myositis, and is frequently associated with anti-ARS antibodies [3].

EMG Is characterized by spontaneous activity at rest (fibrillations, positive sharp-waves and repetitive discharges) and low-amplitude, brief-duration potentials.

Muscle biopsy Muscle biopsy remains the first-choice diagnostic test. In polymyositis, nonnecrotic fibres are invaded by activated CD8+ T cells and by small percentage of macrophages. CD4+ cells are distributed around the fibres without invading them. Macrophages are mainly within necrotic fibres. Almost all fibres express class I HLA antigen on membrane surface. This pattern is not specific of polymyositis and may be observed also in sIBM, which may be distinguished by the presence of vacuoles and inclusions [1].

Muscle magnetic resonance imaging (MRI) may reveal muscle oedema, suggestive of muscle inflammation and help to focus the site of muscle biopsy.

39.2.4 Therapy

See therapy of Myasthenia Gravis – Chap. 37

Treatment of PM is not evidence-based but empirical. Corticosteroids (oral prednisone 1 mg/kg per day, in a single daily morning dose, after breakfast) are the principal treatment. Daily dose is slowly reduced after 3–4 weeks according to efficacy and adverse effects. In patients with severe disease, treatment may start with intravenous methyl-prednisolone at a dose of 1 g per day for 3–5 days and then be switched to the oral prednisone regimen. Azathioprine, methotrexate, mycophenolate mofetil, and ciclosporin can be coadministered. High dose immunoglobulin infusion may be considered.

Rituximab is a further potential therapeutic agent for inflammatory myopathies [8, 9].

39.2.5 Prognosis

There is a worldwide increase in survival of patients with IIM, due to earlier diagnosis and immuno-suppressants. Survival rate of PM patients ranges between 77–92 % and 95 % at 5 and 10 years, respectively. Predictors of poor outcome are higher age, male sex, longer duration of symptoms, presence of cancer, pulmonary disease (particularly interstitial lung disease-ILD), cardiac involvement, dysphagia, and infections.

In the long-term, myositis has a chronic, continuous, or polyphasic course (55–85 %). The presence of auto-AB, particularly of anti-synthetase and anti-signal recognition particle (SRP) is also predictive of poor prognosis.

Another predictor of poor outcome is the treatment based on glucocorticoids alone.

Cardiac involvement and ILD represent the most frequent cause of death [10–12].

In a recent retrospective study on 107 patients with ILD and PM/ DM, ILD was present in 37 % of PM and was more frequently concomitant with PM. In 62 patients, IDL was associated with Jo-1 antibodies. Worsening and poor outcome of ILD were predicted by: (1) older age, (2) presence of ILD symptoms, (3) reduced ventilatory function at the diagnosis of ILD, (4) interstitial pneumonia, and (5) if ILD was nonresponsive to steroids. This study suggests that PM patients, with or without anti-Jo-1 antibody, should be routinely screened for ILD [13].

39.3 Dermatomyositis (DM)

39.3.1 Definition

Dermatomyositis is a systemic inflammatory disorder affecting skeletal muscle and skin due to early activation of the complement cascade, leading to endomysial capillaries destruction and muscle ischemia [9].

39.3.2 Epidemiology

In the United States, the incidence of DM is 1.4 per 100,000 people, with a female and older people preponderance. Juvenile dermatomyositis (JDM) is more common in girls and has a prevalence of 3.2 per 1 million children in the United Kingdom [14].

39.3.3 Clinical Features

Dermatomyositis features are subacute symmetrical proximal muscle weakness, with skin changes, myalgia, and dysphagia (in more severe cases). Dermopathy includes heliotropic (blue-purple discoloration) rash which is most prominent on eyelids, face, upper trunk, knuckles, knees and elbows, and subcutaneous calcifications. The disease is frequently complicated by cancer and ILD [14].

In children with Juvenile DM (JDM), skin disease is more severe, with ulceration or calcinosis; gut vasculopathy or central nervous system disease can cause further threat [15].

Some patients may present skin changes without or with minimal impairment of muscle (clinically amyopathic dermatomyositis, CADM). These patients, which account for 20 % of all DM patients, are at risk for rapidly progressive ILD, particularly in presence of anti-CADM-140 antibody (now termed MDA5). In addition, they may be at increased risk of developing malignancy compared to the general population [16].

39.3.4 Laboratory

Diagnostic work up is the same as PM.

Blood *Autoantibodies* – Include those recognizing Mi-2 (expressed by repairing cells), anti-MDA5 (cytoplasmic RNA-specific helicase that recognize RNA viruses), TIF1γ (the target of the 155 kD autoantibodies described several years ago in DM), and NPX2 autoantibodies (nuclear matrix protein 2). These autoantibodies are useful for both diagnosis and prognosis of DM [17].

Muscle biopsy is characterized by endothelial cells necrosis and reduced numbers of capillaries, with consequent reduced blood supply and perifascicular fibre atrophy; muscle cell degeneration and regeneration are found.

Activation of complement and formation of C5b-9 (MAC), the lytic component of its pathway, is the pathogenetic mechanism of DM. Lymphocytic infiltrates in muscle biopsy (B cells, CD4+ cells, and plasmacytoid dendritic cells in perimysial and perivascular regions) support a humoral-mediated mechanism. Capillaries appear to be positive to MAC [1].

39.3.5 Therapy

See also therapy of Myasthenia Gravis – Chap. 37

Algorithm for treatment of DM is the same as for PM. First line therapy is represented by oral prednisone at the dosage of 1 g/kg/die, associated

with immuno-suppressants: azathioprine, methotrexate, or mycophenolate, to reduce prednisone dosage. If no response is obtained, a therapy with immunoglobulin may be considered. Eculizumab, a monoclonal antibody against complement protein C5, could have a role in treatment of severe DM [9]. Calcinosis of skin or muscle is unusual in adult DM and most frequent in JDM; in severe cases, it may cause muscular retractions [10]. In DM, the most frequently associated malignancies are ovarian (OR 10.5), lung (OR 5.9), and gastrointestinal cancers (OR 3.5). Tumors are more frequent in patients older than 50 years; neoplasms may occur before or during DM, but may also follow the disease.

39.3.6 Prognosis

As for PM, survival of DM patients has improved. The main cause of death is cancer, with no significant differences between PM and DM in disease course, need for continuous therapy, mortality, and quality of life [12].

Patients with anti Mi2 antibodies have a more favorable prognosis, with better response to therapy and less frequent association with cancer. Antibodies against MDA5 are detectable in 13–35 % of DM, particularly in patients with poor or no muscle involvement (CADM). MDA5 positive patients are at increased risk of ILD and oral ulceration and arthralgia. A review of cancer-associated DM showed that patients with anti-155 kD antibodies (targeting TIF1γ) had an 89 % specificity and a 78 % sensitivity for diagnosis of cancer-associated DM.

NXP2 antibodies are detected in patients with severe muscle impairment, arthritis, joint contractures, and intestinal vasculitis. They were also found in 23–25 % of JDM with calcinosis [17].

Final note Although pathogenetic mechanisms leading to PM and DM are different, immunosuppressive treatment is the same for both diseases and systemic complications (cardiac and pulmonary function impairment, dysphagia, joint manifestations, association with cancer) are commonly observed both in PM and DM. For these reasons, most studies on follow-up of IIM have been conducted by rheumatologists on series of patients affected both by PM and DM. Therefore, results from these studies apply to the whole group of PM/DM patients, with no distinction between the two disorders. Accordingly, survival rates in PM/DM patients at 5 years vary from 52 to 95 % and, after 5 years, percentages of survival vary between 32 and 89 %. This variability may be due to patient selection criteria. For example, in the paper by Sultan and colleagues, among 46 selected patients, 50 % were PM, 30 % were adult-onset DM, one was JDM, 17 % had a systemic lupus erythematosus or rheumatoid arthritis associated with myositis. In this series, patients with cancer-associated PM/DM were excluded [18].

From studies of PM/DM patients, it appears that prognosis is still poor, complete remission is reached only by a small percentage of patients, and the overall mortality is threefold higher than in normal population. Cancer, ILD, and cardiac involvement are the most frequent causes of death [10].

39.4 Necrotizing Autoimmune Myopathy (NAM)

39.4.1 Definition

Necrotizing autoimmune myopathy is an inflammatory myopathy characterized by fibre necrosis and by the presence (60 % of patients) of autoantibodies against signal recognition particles (sRP) or 3-hydroxy-3-methylglutaryl co-enzyme A reductase (HMGCR).

39.4.2 Epidemiology

From data collected in small groups of patients, the disease peaks between ages 50 and 60 years, and has a male preponderance.

39.4.3 Clinical Features

It is similar to those of PM, with acute or subacute generalized muscle wasting and weakness,

often associated with respiratory failure or dysphagia.

39.4.4 Laboratory

Blood CK levels are very high (up to 1000 normal values).

EMG shows abundant spontaneous activity at rest and small amplitude short duration units.

Muscle biopsy is mandatory for the diagnosis. HLA I positive, necrotic fibres surrounded by sparse mononuclear cells, mainly macrophages and few CD4+ and CD8+ T lymphocytes are found [17].

39.4.5 Therapy

Patients usually respond to high prednisone dosage and should be treated according to the algorithm proposed for PM and DM.

39.4.6 Prognosis

There are no longitudinal studies on morbidity and mortality of NAM and until now few patients have been reported.

39.5 Inclusion Body Myositis (IBM)

39.5.1 Definition

Inclusion Body Myositis is the most common sporadic myopathy over the age of 50 years and is characterized by both inflammatory and degenerative aspects. It is also named sporadic IBM (sIBM) to distinguish this form of disease from hereditary inclusion body myopathies (hIBM), which share with sIBM degenerative but not inflammatory pathogenetic mechanisms.

39.5.2 Epidemiology

The incidence of IBM varies among different countries and has increased in the last years probably due to the improvement of diagnosis. In 2006, the incidence of IBM in Western Australia was 13 per million (39.5 per million in males over 50 years) [19].

39.5.3 Clinical Features

The disease has a subacute onset of symptoms and a slowly progressive evolution. The typical phenotype includes early atrophy and weakness of quadriceps and fingers flexors of hands, often asymmetric, and dysphagia. Less common phenotypes include head drop and camptocormia, caused by weakness of paraspinal muscles, and in some cases facial muscles involvement. Dysphagia, due to abnormal hyoid-laryngeal excursion is present in 65–80 % of patients, and may be the prominent deficit [14]. Differently to other IIM, IBM is not usually associated with cancer.

Blood CK is usually mildly increased (three to four times above the standard limit) but is normal in some patients.

EMG As in other IIM, presents myopathic motor unit potentials and spontaneous activity at rest.

Muscle biopsy evidentiates endomysial infiltrates of CD8+ and macrophages invading non-necrotic fibres and HLA I expression on fibre sarcolemma. In addition to inflammatory aspects, there are also degenerative features such as vacuoles (rimmed vacuoles), inclusion containing β-amyloid and other proteins as p-tau, presenilin 1, TDP 43 [19, 20].

39.5.4 Therapy

Corticosteroids and other immunosuppressive drugs are not useful in this disorder. A small

percentage of patients are partially responsive to steroids, particularly in the early phase of the disease. Intravenous administration of immunoglobulin may reduce swallowing disturbances. Cricopharyngeal myotomy, pharyngo-esophageal dilation, and injection of botulinum toxin have been proposed on the hypothesis of an abnormal oesophageal sphincter relaxation at the base of dysphagia.

39.5.5 Prognosis

The disease is progressive and most patients need support to walk within 5 years after onset and are wheelchair-bound after 10 years. Dysphagia may become very severe and often requires percutaneous gastrostomy. If untreated, swallowing abnormalities may cause ab ingestis pneumonia or cachexia, which are the most frequent causes of death [20].

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Neurological Pain

40

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Abbreviations

CBZ, carbamazepine; CLBP, chronic low back pain; CPSP, central post-stroke pain; CRPS, complex regional pain syndrome; FIESTA, fast imaging employing steady-state acquisition; GN, glossopharyngeal neuralgia; TN, trigeminal neuralgia

40.1 Introduction

Neuropathic pain affects about 5 % of the population and 40 % of patients with a neurological disease [1]. It can follow central and/or peripheral nervous system diseases, leading to distinct clinical pictures that reflect anatomic-functional impairment through the somatosensory pathway. Its definition has been recently revised in response to the need of more narrow criteria for the clinical practice and the differential diagnosis with other forms of pain [2]. The current definition of neuropathic pain is that of a "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system." It has introduced a novel concept that the prerequisite for the diagnosis of neuropathic pain is the identification of an injury or dysfunction in a structure involved in the transduction and perception of sensation, from the most distal nerve fibers in the skin to the brain. A grading system has also been introduced to provide a level of certainty regarding the diagnosis of neuropathic pain, from possible to probable and definite based on the plausibility of the distribution of symptoms and signs and the demonstration of their relationship with the lesion or disease by using validated confirmatory tests (e.g., neurophysiological or neuropathological exams). Overall, this approach emphasized the need for an adequate diagnostic work-up in all patients that should help physicians identify the etiology of neuropathic pain and facilitate the choice of disease-modifying treatments besides symptomatic therapies. Examples of how this approach can impact patient care are painful paraneoplastic, immune-mediated, and vasculitic neuropathies [3, 4], in which a delay in the diagnosis may mean a delay in initiating life-saving therapies. Moreover, patients not meeting the criteria for neuropathic pain can differentiate diagnostic work-up, including rheumatologic and psychiatric evaluations, in order to identify appropriate therapies.

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Overall, the prognosis of neuropathic pain depends of the pathogenesis of the underlying diseases and is influenced by a number of factors, including mood (e.g., depression, anxiety, catastrophizing) and cognitive context (e.g., hypervigilance, expectation). Research has been providing compelling findings on the susceptibility to develop pain, opening novel scenarios on individual genetic signatures and tailored pharmacological treatments that would change short and long-term prognosis of neuropathic pain in patients [5–8].

40.2 Trigeminal and Other Cranial Neuralgias

Key Facts

- **Terminology and definitions** – Neuralgias are characterized by short lasting, paroxysmal, electric shock-like pain restricted within the sensory territory of a single peripheral nerve.
- **Clinical features**
  - **Trigeminal neuralgia** (**TN**): estimated incidence 4–13,5/100,000/year. Pain is limited to the distribution of one or more branches of the trigeminal nerve; typically lasts from seconds up to a few minutes and is often followed by a brief refractory period. In most patients, attacks are triggered by trivial stimuli.
  - **Trigeminal terminal branches**: incidence not known. They are diagnosed according to the localization of pain that presents with the typical features of neuralgia.
  - **Glossopharyngeal neuralgia** (**GN**): estimated incidence =0.7/100,000/year. Sharp, stabbing pain within the posterior part of the tongue, beneath the angle of the lower jaw, and/or in the ear that is elicited by swallowing, chewing, talking, coughing, or yawning.
- **Imaging**
  - **Brain CT scan, brain MRI** – To rule out CNS and PNS lesions. To demonstrate neurovascular conflicts.
- **Top differential diagnoses –** Multiple sclerosis, brainstem tumors, vascular diseases, syrinx, paroxysmal migraine
- **Principles of treatment**
  - **Medical** – First line: CBZ and oxcarbazepine.
  - **Surgical** (trigeminal neuralgia): microvascular decompression, radiofrequency rhizotomy, glycerol rhizolysis, balloon compression, and gamma knife stereotactic radiosurgery.
  - **Topical** (trigeminal terminal branches): anesthetic block.
- **Prognosis**
  - **Medical treatment outcome** (TN): often progressive; spontaneous remission is possible. CBZ obtains 100 % of pain relief in about 70 % of patients. In the long term, 50 % of TN patients become refractory to medical treatment and require surgery.
  - **Surgery outcome**: (1) **micro-vascular decompression**: complete relief: 80 % at 1 year, 75 % after 3 years, 73 % after 5 years. (2) *Radiofrequency rhizotomy*: 68–85 % pain-free patients at 1 year, 54–64 % after 3 years, 50 % after 5 years. (3) *Glycerol rhizolysis*: immediate pain relief in 90 % of patients; 61 % and 50 % of pain-free patients at 1 and 3 years. (4) *Balloon compression*: Immediate pain relief in 90 % of patients. Recurrence rate of 28 % in the second year after the treatment. (5) *Gamma knife stereotactic radiosurgery*: pain relief in 75 %, 60 %, and 58 % at 1, 3, and 5 years, respectively.

40.2.1 Definition

Neuralgia is a condition characterized by short lasting, stereotyped, paroxysmal, electric shock-like pain attacks that are restricted within the sensory territory of a single peripheral nerve. In certain conditions, pain attacks can be provoked by non-painful stimuli (e.g., light touch or pressure) or simple actions (e.g., chewing, swallowing, blowing the nose, turning the head, sneezing). They are followed by a period without symptoms called "refractory period," which tends to shorten as the disease progresses.

40.2.2 Trigeminal Neuralgia

40.2.2.1 Clinical Features

Trigeminal neuralgia (alias *tic douloureux*) is the most frequent among cranial neuralgias. The estimated annual incidence ranges between 4 and 13.5/100,000 [8] with slight female predominance. The incidence gradually increases with age and is rare below 40 years of age. It is more common in patients with multiple sclerosis and hypertension may be a risk factor in women. The International Association for the Study of Pain defines trigeminal neuralgia as a unilateral painful disorder characterized by recurrent attacks of brief, electric-shock-like pain with abrupt onset and termination, limited to the distribution of one or more branches of the trigeminal nerve. The revised International Classification of Headache Disorders-3 (ICHD-3) suggested three variants:

1. *Classical trigeminal neuralgia*, often caused by microvascular compression at the trigeminal root entry to the brainstem
2. *Trigeminal neuralgia with concomitant persistent facial pain*
3. *Symptomatic trigeminal neuralgia*, caused by a structural lesion other than vascular compression

Pain typically involves one single trigeminal nerve branch, most frequently the second or third one. It typically lasts from seconds to a few minutes and is often followed by a brief refractory period. In most patients, trigeminal neuralgia can be triggered by trivial stimuli such as cold air, talking, chewing, brushing teeth, or light touch to the skin. These trigger areas on the face, nose, and lips can be very small (1–2 mm) and their recognition may help in the diagnosis. When trigeminal neuralgia involves the second and in particular the third branch, pain attacks can be so severe to interfere with eating and can lead to loss of body weight.

Idiopathic trigeminal neuralgia is diagnosed on clinical ground based on the patient's history and normal neurological examination. The presence of facial numbness, sensory loss, allodynia, or other neurological signs should suggest a secondary form.

Brain magnetic resonance imaging (MRI) is mandatory to rule out central nervous system lesions, including multiple sclerosis, brainstem tumors or infarctions, and syringobulbia [9, 10]. Specific sequences (e.g., fast imaging employing steady-state acquisition) and 3-D reconstruction images are warranted to identify a neurovascular conflict between the trigeminal nerve and a brainstem vessel.

40.2.2.2 Prognosis

Natural History

Trigeminal neuralgia causes severe pain that usually requires medical interventions. Therefore, information about the natural course of the disease is scarce. Spontaneous remission is common, but the disorder is often progressive. Remission may last for months or even years but, as the attacks become more frequent, the patient may develop persistent pain between episodes.

One retrospective study performed in Rochester over a 40-year period reported that 29 % of patients had only 1 episode of pain, 19 % had 2, 24 % had 3, and 28 % had 4 to 11. The interval between the attacks was variable, with 65 % of patients having the second episode within 5 years from the first, whereas 23 % of patients had more than 10 years free of pain. Similar ranges of delay were reported from the second to the third attack.

Medical Treatment Outcome

The accepted definition of successful treatment is 50 % of pain relief and 75 % of attack reduction. Carbamazepine (200–1200 mg/day) and oxcarbazepine (600–1800 mg/day) are the first-line treatments, according to current evidence-based guidelines. Carbamazepine can provide up to 100 % of pain relief in about 70 % of patients. However, response is not constant and over time fewer patients continue to have sustained pain relief. This may also be related to changes in the pharmacokinetic of the drug, whose half-life reduces over time at long-lasting dosage regimen. About 5–19 % of individuals are intolerant to carbamazepine. Side effects affecting the

central nervous system (i.e., drowsiness, dizziness) usually lessen after a few days of treatment. Cognitive impairment, severe dermatologic reactions, and bone marrow suppression represent the most relevant and even life-threatening adverse events. A strong correlation between HLA-B*1502 allele and carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis has been described in Asiatic populations. The efficacy of oxcarbamazepine relies less on evidence-based studies.

Patients with intolerable side effects or poor response should undergo second-line treatment, such as add-on therapy with lamotrigine (400 mg/day) or switch to lamotrigine or baclofen (40–80 mg/day). However, evidence on responsiveness is small. Other antiepileptic drugs (e.g., phenytoin, gabapentin, pregabalin, and valproate) have been studied in small open-label studies and their use can be considered, though data on efficacy are not proven. There are no published studies comparing polytherapy with monotherapy. Referral for a surgical consultation is warranted in patients with trigeminal neuralgia refractory to medical treatment, which occurs in about 50 % of patients.

Surgical Treatments Outcome

The main surgical option for trigeminal neuralgia is microvascular decompression that aims to treat the cause of the disorder. Palliative percutaneous destructive procedures include radiofrequency rhizotomy, glycerol rhizolysis, balloon compression, and gamma knife stereotactic radiosurgery, which aim to achieve pain relief through a controlled damage of trigeminal neurons or nerve root. Based on the balance between recurrence rate and side effects, microvascular decompression is considered the first-line surgical option. It provides a higher chance of complete drug-free pain relief (about 80 % of cases) with the lowest recurrence rate (10 % in 10 years). Palliative destructive procedures showed a recurrence rate ranging from 25 to 50 % in 3–5 years, and more frequent side effects like facial numbness and sensory loss. Significant predictors of recurrence include female gender, lack of immediate pain relief, and symptoms lasting more than 8 years.

1. *Microvascular decompression* – It can provide satisfactory control of pain, with up to 90 % of patients achieving immediate pain relief, more than 80 % remaining pain-free after 1 year, 75 % after 3 years, and 73 % after 5 years. It is a major surgical procedure in which craniotomy is performed to reach the trigeminal nerve in the posterior fossa. The average mortality rate ranges from 0.2 to 0.5 %. Up to 4 % of patients can experience major adverse events including cerebrospinal fluid leakage, infarcts, hematomas, or aseptic meningitis, besides general anesthesiologic risks. Hearing loss can occur in less than 3 % of patients, whereas facial numbness or dysesthesia have been reported in less than 1 % of patients [9, 11].
2. *Radiofrequency rhizotomy* – Also known as "thermal rhizotomy," it is based on heat radiations that selectively destroy nociceptive Aδ and C fibers. It provides immediate pain relief in more than 90 % of patients. At 1-year follow-up, 68–85 % of patients are still pain free, but after 3 years the percentage reduces to 54–64 % and after 5 years only 50 % of patients are still pain free. The recurrence rate of trigeminal neuralgia after 14 years is about 25 %. Side effects are not rare and include dysesthesias in 20–30 % of patients, corneal sensory loss in 20 %, and anesthesia dolorosa in 1–5 %. About half the patients can complain of transient weakness of trigeminal innervated muscles, which usually resolves in 3–6 months.
3. *Glycerol rhizolysis* – It is performed by the percutaneous injection of glycerol into the Gasserian ganglion. The injection is made about 2.5 cm lateral to the corner of the mouth under topical anesthesia. About 20 % of patients experience a vasovagal response to transovale needle penetration or to the glycerol injection. At the end of the procedure, the patient is kept semi-sitting to avoid glycerol linkage into the posterior fossa. About 90 % of patients experienced immediate pain relief. The recurrence rate varies among the studies, ranging from long-lasting pain relief in 77 % of patients, with 55 % discontinuing all medi-

cations and 22 % requiring some drug after 11 years, to 61 and 50 % of pain-free patients without medications at 1 and 3 years, respectively [12]. One study reported a mean time interval of 22 months until the need of repeated treatments up to the fifth injection, and 6 months in patients requiring their sixth injection. Among patients requiring repeat injections within 6 months, 23 % had multiple sclerosis. Facial numbness occurred in 9 % of patients, but increased to 16 % after repeated treatments. About 10–20 % of patients can develop reduction in light touch or pinprick (pain) perception, which is usually mild. After two or three procedures, 50–70 % of patients can present mild to moderate sensory loss.

4. *Balloon compression* – This procedure requires general anesthesia and is performed under X-ray control by an inflating catheter that compresses the Gasserian ganglion. The duration of inflation ranges from 1 to 5 min. Immediate pain relief is reported in about 90 % of patients, with a recurrence rate of 28 % in the second year after the treatment. Side events include mild sensory loss in 80 % of patients, transient weakness of masseter muscle in 16 %, and aseptic meningitis in 5 %.
5. *Gamma knife stereotactic radiosurgery* – This is one of the most recent and less invasive techniques available for treating trigeminal neuralgia. It uses a radiation beam concentrated on the trigeminal root in the posterior fossa. Unlike other treatments, stereotactic radiosurgery is unlikely to provide immediate pain relief and usually requires a mean latency period of 1 month before symptoms improvement. In a large study on 450 patients [13], it was reported to provide adequate pain relief in 75 %, 60 %, and 58 % of idiopathic trigeminal neuralgia patients at 1, 3, and 5 years, respectively. Among patients with multiple sclerosis, 56 %, 30 %, and 20 % patients achieved satisfactory pain relief at 1, 3, and 5 years, respectively. Repeated treatment provided pain relief in 75 % of idiopathic cases and 46 % of multiple sclerosis patients at 5 years. Mild facial numbness was reported by 6 % of patients after the first treatment and by 24 % after repeated treatment. Severe facial numbness was rare (0.5 % after the first and 2 % after the second treatment).

40.2.3 Neuralgia of Trigeminal Nerve Terminal Branches

Injuries of terminal branches of the trigeminal nerve, including infraorbital, lacrimal, lingual, alveolar, and mental nerves, can cause paroxysmal pain referred to specific areas.

Lesions of the nasociliary nerve, a branch of the ophthalmic nerve, cause the so-called *Charlin's neuralgia*. The nasociliary nerve enters the cranial cavity above the cribriform plate of the ethmoid bone, supplies branches to the mucous membrane of the nasal cavity, and emerges between the inferior border of the nasal bone and the side nasal cartilages. Neuralgia is typically triggered by light touch on the outer aspect of the nostril. Stabbing pain can last seconds to hours and radiated upward to the medial frontal region. Treatment is based on the block or section of the nasociliary nerve, or application of topical anesthetics to the affected nostril.

Lesions of the supraorbital nerve, a terminal branch of the frontal nerve arising from the ophthalmic nerve, cause the *supraorbital neuralgia*. The supraorbital nerve supplies upper eyelid, conjunctiva, frontal sinus, and the skin of the forehead up to the middle of the scalp. Neuralgia is characterized by paroxysmal pain involving the region of the supraorbital notch and medial aspect of the forehead. Treatment is based on local anesthetic block of the supraorbital nerve.

40.2.4 Glossopharyngeal Neuralgia (GN)

40.2.4.1 Clinical Features

Glossopharyngeal neuralgia is an uncommon facial pain syndrome with an estimated incidence of 0.7 cases per 100,000 inhabitants per year. The clinical picture must fulfill the following criteria: (1) sharp,

stabbing, and severe pain; (2) pain precipitated by swallowing, chewing, talking, coughing, or yawning; (3) pain distribution within the posterior part of the tongue, tonsillar fossa, pharynx, or beneath the angle of the lower jaw and/or in the ear. Trigger areas can be identified in the neck and external auditory canal. Symptomatic glossopharyngeal neuralgia may present with deep pain persisting between attacks, associated with sensory impairment within the distribution of the glossopharyngeal nerve [10, 14]. A symptomatic form can be caused by oropharyngeal malignancies, peritonsillar infection, or vascular compression.

40.2.4.2 Diagnosis

The diagnostic work-up should include a magnetic resonance of the head and neck. When symptoms like bradycardia, hypotension, or syncope occur (about 2 % of patients), the syndrome may be called "vagoglossopharyngeal neuralgia." These symptoms are explained by the crossover between glossopharyngeal and vagus nerves.

40.2.4.3 Medical and Surgical Treatments Outcome

Medical treatment is based on the same drugs used for trigeminal neuralgia, such as carbamazepine and oxcarbazepine as first-line and phenytoin, baclofen, gabapentin, and pregabalin as second-line.

Surgical options should be considered in non-responder patients.

Microvascular decompression was reported to provide long-term pain relief in about 90 % of patients with low rate of recurrence and complications such as dysphagia or hoarseness. Other surgical procedures, including radiofrequency rhizotomy and stereotactic radiosurgery, have been performed with good results [10].

40.2.5 Geniculate Neuralgia

40.2.5.1 Clinical Features

Geniculate neuralgia is caused by lesions of the nervus intermedius, also known as "Wrisberg nerve." It carries parasympathetic fibers to the lacrimal and nasopalatine glands and sensory information from areas of the tongue, nose, and ear. A cutaneous branch arising close to the chorda tympani nerve joins with the auricular branch of the vagus nerve to supply the external auditory canal and concha of the external ear. This innervation allows the identification of herpetic vesicles in the ear after the infection in the geniculate ganglion in the Ramsay–Hunt syndrome. Geniculate neuralgia presents with brief paroxysmal pain, lasting for seconds or minutes, deeply in the auditory canal. The posterior wall of the auditory canal may be a trigger area. Altered lacrimation, salivation, and taste abnormalities can accompany pain. Inferior cerebellar artery compression can cause the syndrome. Glossopharyngeal neuralgia with primarily otalgia may mimic geniculate neuralgia.

40.2.5.2 Medical and Surgical Treatments Outcome

Medical approach is similar to that of trigeminal neuralgia. However, data derive from anecdotal patients and small case series.

Surgical treatments include microvascular decompression, nervus intermedius sectioning, and geniculate ganglion resections. Overall, surgical treatments provided pain relief in up to 75 % of patients followed for a period ranging from 3 to 15 years. Hearing loss, decreased lacrimation, salivation and taste, tinnitus, and vertigo are possible long-term complications [15].

40.2.6 Superior Laryngeal Neuralgia

40.2.6.1 Clinical Features

The superior laryngeal nerve arises from the vagus nerve below the ganglion nodosum. It runs along the side of the pharynx and ends in the internal and external branches. The internal branch carries fibers through the thyrohyoid membrane to the mucous membrane of the larynx and communicates with the recurrent laryngeal nerve. The external branch supplies motor fibers to the cricothyroid muscle. Superior laryngeal neuralgia is a rare disorder characterized by severe pain in the lateral aspect of the throat, submandibular region, and underneath the ear, triggered by swallowing, shouting, or turning the head.

Seasonal occurrence in the fall and winter months has been reported. Pain is typically elicited by pressure over the entry point of the superior laryngeal nerve through the thyrohyoid membrane and is strongly supportive of the diagnosis. Symptomatic form can be caused by carotid artery surgery, deviation of the hyoid, tonsillectomy, pharyngeal diverticulum, and trauma.

40.2.6.2 Medical and Surgical Treatments Outcome

Carbamazepine has been successfully used, providing in most patients good effectiveness with short-term treatment. Local anesthetic injections and nerve sectioning have been used in non-responder patients [16].

40.2.7 Occipital Neuralgia

40.2.7.1 Clinical Features

It is an uncommon cause of paroxysmal pain involving the territory of the greater, lesser, or third occipital nerve. All are spinal nerves originating from the second (sometimes also third) cervical root. The greater occipital nerve runs through the trapezius muscle and ascends to innervate the skin on the posterior part of the scalp up to the vertex, the ear, and the parotid gland. The lesser occipital nerve is one of the four cutaneous branches of the cervical plexus and innervates the scalp in the lateral area of the head posterior to the ear, whereas its terminal auricular branch supplies the skin of the upper and back part of the auricula.

The frequency of occipital neuralgia is not known. In most cases, it remains an idiopathic condition, although cervical whiplash, traumatic injuries, and vascular compression have been reported. The clinical picture is typically characterized by paroxysmal pain described as stabbing, shooting, electric, or "shock-like," which originates in the occiput and radiates toward the vertex.

Different types of primary headaches and C2 neuralgia should be considered in the differential diagnosis.

40.2.7.2 Medical and Surgical Treatments Outcome

Medical treatment with tricyclic antidepressants and antiepileptics may be useful but there is not enough evidence.

Surgical treatments

Anesthetic block was reported to provide immediate pain relief lasting up to 2 week in 90 % of cases and 1 month in 10 %.

Botulinum toxin type A injection showed a mean duration of pain relief for 16 weeks.

Pulsed radiofrequency reduced pain intensity by 50 % in half the patients at 3-month follow-up. Subcutaneous occipital nerve stimulation provided satisfactory pain control in up to 80 % of patients over a follow-up period ranging from 18 months to 6 years. Medically intractable occipital neuralgia patients can be selected for surgical removal of C2 and C3 cervical sensory dorsal root ganglion. This surgical option has been tested on a small series of patients producing pain relief at short-term follow-up (<3 months), with 65 % recurrence rate at 12 months [17].

40.3 Chronic Low Back Pain (CLBP)

Key Facts

- **Terminology and definitions** – CLBP is a pain of variable duration, not caused by a known disease.
- **Clinical features** – Estimated prevalence of CLBP is 65 % in 1 year and 84 % in lifetime. It can have an acute (<6 weeks), sub-acute (6 weeks–12 weeks), and chronic (>12 weeks) course.
- **Imaging** – CT scan or MRI of the spine
- **Top Differential Diagnoses** – Spondyloarthritis, discitis, lumbar spine stenosis, ankylosing spondylitis, myeloproliferative diseases, traumatic bone injuries, fractures
- **Principles of treatment** – NSAD, opioids, antidepressants, physiotherapy. Surgery may be considered after at least 2 years of adequate but unsuccessful medical treatments.
- **Prognosis** – Low back pain commonly improves in the first month; 20–30 % of patients can to complain of symptoms after months or years

40.3.1 Definition

Chronic low back pain (CLBP) is a condition conventionally referring to pain of variable duration in the lumbar region. This definition excludes all those cases in which pain is caused by a known disease like trauma, fractures, infections, neoplasms, or other identified conditions.

CLBP is classified according to its duration as acute (<6 weeks), sub-acute (6 weeks–12 weeks), and chronic (>12 weeks). Many patients suffering from CLBP experience waxing and waning of symptoms, making such a narrow classification not useful in clinical practice. This may also explain why most epidemiological studies did not distinguish between CLBP persisting for more or less than 1 year.

40.3.2 Epidemiology

The estimated frequency of CLBP varies considerably between studies, from 33 % of point prevalence to 65 % of 1-year prevalence and 84 % in lifetime. Aging does not appear to increase the prevalence. CLBP likely affects about 25 % of the general population, though approximately 80 % of people will experience at least one episode of acute back pain during lifetime.

40.3.3 Diagnosis

Patients complaining of CLBP for more than 6 weeks, or who further deteriorate between 6 weeks and 3 months, should be re-considered for specific etiologies, including chronic inflammatory diseases, such as spondyloarthropathy and ankylosing spondylitis, and myeloproliferative diseases. Spine disorders such as facet syndrome and lumbar stenosis should be considered. Appropriate diagnostic work-up should be performed based on personal history and clinical examination. The diagnostic work-up includes X-ray, CT scan, and MRI. Neurophysiological exams (nerve conduction study, electromyography, somatosensory evoked potentials) can be considered to rule out nerve, root, and spinal cord dysfunctions.

40.3.4 Treatments and Prognosis

The therapeutic approach to CLBP is not standardized and remains relatively unspecific, resulting in a broad variety of pharmacological, physical, chiropractic, and cognitive behavioral therapies whose effectiveness has not been validated by evidence-based data. Different guidelines have been published. Overall, patients should be reassured on the benign prognosis of the condition, emphasizing the need to stay as active as possible, to progressively increase their activity level and to return to work as soon as possible, despite some low back pain [18].

Paracetamol/acetaminophen should be used as first-line therapy to manage patients in the acute phase. NSAID can be effective in the acute phase, but their chronic use should be avoided due to the high rate of side effects. Muscle relaxants may be effective for short-term pain control especially when combined with NSAID. There is evidence of short-term efficacy of tramadol and strong opioids (morphine, hydromorphone, oxycodone, oxymorphone, tapentadol), whereas long-term efficacy and safety are unproven. Opioids and antidepressants showed similar efficacy in two trials [19]. Among antidepressants, duloxetine received Food and Drug Administration (FDA) approval for the treatment of chronic musculoskeletal pain including CLBP [20]. Treatment with corticosteroids lacks evidence on efficacy, can cause severe side effects, and should be avoided. Surgery should be considered only in those patients suffering from CLBP caused by a defined spine disease or when pain is not controlled after at least 2 years of adequate medical treatments.

The course of CLBP is benign and most commonly pain and disability improve quickly within the first month in the majority of patients. Acute lumbar pain is often monophasic, though it relapses in 50–80 % of patients within the first year. In 90 % of cases, pain recovers within 6 weeks, but in 2–7 % of patients it becomes

chronic. About 20–30 % of patients may continue to complain of symptoms after several months or years from the onset. Lumbar pain may be associated with sciatic pain for which there is most commonly no evidence of root lesion at CT scan and MRI. About 70 % of patients can return to work within 1 week from the acute onset and 90 % within 2 months. However, it has been reported that 15 % of those initially unable to work may not be working after 1 year. The longer is the period of suspension from work, the lower is the probability that the patient will return to work. Only 50 % of patients who did not return to work within 6 months from the pain attack will do, and nearly none of those who did not have returned for 2 years.

40.4 Sciatica (Lumbar Disk Herniation)

Key Facts

- **Terminology and definitions** – Dermatomeric pain with a distribution on the posterior or lateral regions of one of both lower limbs
- **Clinical features** – Sensory (hypoesthesia, paresthesia, pain) and motor (muscle wasting and weakness) disturbances with dermatomal and myomeric distribution
- **Imaging** – CT scan and MRI of the lombar spine have similar sensitivity and specificity
- **Top Differential Diagnoses** – Arthrosis, cauda equina syndrome, lumbar spine stenosis, neoplasms, inflammatory diseases
- **Principles of treatment**
  - **Medical** – Non-steroidal anti-inflammatory drugs, analgesic drugs.
  - **Surgery** – Discectomy or micro-discectomy at least 6–8 weeks after onset
- **Prognosis**– 50 % of patients improve within a month from the onset and 90 % within 6–12 weeks. Large herniations can reabsorb better. Discectomy is faintly superior to conservative treatment in the first 2–4 years after surgery

40.4.1 Definition

The term "sciatica" refers to pain distributed on the posterior or lateral region of the lower limb. It can be associated with sensory and/or motor deficits.

40.4.2 Epidemiology

Acute lumbar disk herniation is the most common cause of sciatica in western countries, with an estimated annual prevalence of 1–3 %. About 95 % of disk herniation involves L5 or S1 roots.

Disk degeneration or bulging can be found in 35 % of subjects aged 20–39 years; lumbar spine abnormalities are found in 57 % of subjects aged 60 years or older without history of low back pain. Lumbar radicular syndrome has a great socioeconomic impact and is one of the most important causes of ours of work missed.

40.4.3 Clinical Features

The distribution of sensory symptoms and motor defects reflect the dermatomeric and myomeric innervation, allowing the differential diagnosis with mononeuropathy or plexopathy. Pain may be enhanced by Valsalva maneuver. In patients with motor impairment, weakness and knee deep tendon reflex can be absent in L3 and L4 radiculopathy and Achilles tendon reflex in S1 radiculopathy. Femoral stretch test and Lasègue sign can be positive in proximal (L1, L2, L3, L4) and distal (L5, S1) radiculopathies, respectively.

40.4.4 Differential Diagnosis

Nerve conduction study showing normal amplitude of sensory nerve action potential differentiate pre-ganglionic damage typical of disk herniation (e.g., saphenous nerve in L4, superficial

peroneal nerve in L5, and sural nerve in S1 radiculopathies) from ganglionic or post-ganglionic damage typical of sensory neuronopathy and neuropathy. Ventral root damage can cause the decrease of compound motor action potential amplitude. Needle electromyography (EMG) can show spontaneous activity and chronic neurogenic changes of motor unit potentials in paraspinal muscles and in proximal and distal muscles with same root innervation (e.g., gluteus medium and peroneus longus in L5 and gluteus maximum and gastrocnemius in S1 radiculopathies). Radiculopathy can cause clinical and EMG impairment of muscles innervated by the same root but different nerve truck, allowing the differential diagnosis with mononeuropathy (e.g., tibialis anterior muscle innervated by peroneal nerve and tibialis posterior muscle innervated by posterior tibialis nerve receive innervation by L5 root).

CT scan and MRI are mandatory for the diagnosis and have the same reliability.

40.4.5 Medical Approach of the Acute Phase

Bed rest is the first line approach in order to limit mechanical overload of the compressed root in the acute phase (<6 weeks). Non-steroidal anti-inflammatory drugs, acetaminophen, muscle relaxants, and systemic corticosteroids (e.g., dexamethasone 8 mg i.m. for 8 days) can be used to achieve the control of symptoms and pain relief.

40.4.6 Surgery

Open discectomy and endoscopic discectomy are the gold standard surgical techniques. A recent meta-analysis of existing clinical trials suggested that endoscopic discectomy is a safe supplementation and alternative strategy to standard open discectomy [21]. Patients are usually evaluated for surgery if symptoms do not improve after 6 weeks of conservative treatments. About 10 % of patients are estimated to fall into this category. Surgery can achieve faster pain relief with a median time to recovery of 4 weeks in case of discectomy, compared to 12 weeks with medical treatments.

40.4.7 Prognosis

Most disk lesions are asymptomatic and long-term control of symptoms may occur irrespective of herniation recovery. Sequential MRI studies demonstrated that disk herniation, better if large, can spontaneously reabsorb with a complete recovery in 65 % of cases at 6 months.

In the absence of major neurological deficits (e.g., motor weakness, refractory pain), 50 % of patients can improve with minor conservative treatments within 1 month from onset and 80 % within 6–12 weeks. The long-term efficacy of discectomy compared with conservative treatment remains uncertain. Discectomy has a better outcome in patients under 40 years of age, if duration of symptoms is shorter than 6 months and in cases with severe pain. A randomized trial with 5-year follow-up design [22, 23] showed that early surgery can provide faster recovery of symptoms and better outcome at 1 month. However, at 6 months both surgically and conservatively treated subjects showed the same rate of recovery that remained comparable up to 5 years of follow-up. About 20 % of patients continued suffering of sciatica also after 5 years. Among prognostic factors, high amount of pain (VAS ≥7), age over 40 years, depression, and a more anxious mood are the most predictive of an unsatisfactory surgery outcome. Among patients who underwent lumbar disk surgery, 3–6 % had adverse events including wound infection, spondylodiscitis, meningitis, dural perforation, or radicular lesion. Re-intervention was required in 3–15 % of cases with an overall risk of death of 0.5–1.5/1,000 at 1 month after surgery. Clinically silent relapse of disk herniation is common even after lumbar discectomy.

A recent study [24] demonstrated that MRI performed at 1-year in patients who had been treated for sciatica and lumbar-disk herniation did not distinguish between those with a favorable outcome and those with an unfavorable outcome.

40.5 Complex Regional Pain Syndrome

Key Facts

- **Terminology and definitions** – Disorder characterized by pain, autonomic, trophic, and motor abnormalities. CRPS type I is also known as "reflex sympathetic dystrophy"; CRPS type II is also known as "causalgia."
- **Clinical features** – Estimated incidence of CRPS is 5–26/100,000/year. Symptoms include hyperesthesia, temperature asymmetry, edema, motor dysfunction. No specific laboratory exam exists.
- **Imaging** – X-ray to demonstrate regional osteopenia; CT scan; 3-phase bone scintigraphy.
- **Top Differential Diagnoses** – Neuropathic pain syndromes; vascular diseases; inflammatory and myofascial disorders; psychiatric diseases.
- **Principles of treatment** – Bisphosphonates to inhibit bone reabsorption; antiepileptic, antidepressant, and opioids for pain. Sympathetic block and sympathectomy in selected cases.
- **Prognosis** – Highly variable: improvement in 6–12 months with minimal sequelae in some patients. Pain, skin trophic changes, and motor symptoms can persist for years.

40.5.1 Definition

The complex regional pain syndrome (CRPS) is a condition characterized by pain, autonomic, trophic, and motor abnormalities involving the distal extremity of one limb. The International Association for the Study of Pain has classified CRPS in type I and type II, formerly known as "reflex sympathetic dystrophy" and "causalgia," respectively. The classical distinction between these two conditions is based on the evidence of a nerve injury in CRPS II but not in CRPS I. However, this distinction has been argued because tissue injuries and surgery can damage peripheral nerve endings (e.g., nociceptive small diameter skin nerve fibers) [25].

40.5.2 Epidemiology

The incidence of CRPS has been estimated between 5 and 26 per 100,000 persons/year. In adults, it more often involves the upper extremities (60 % of cases). Women are about three to four times more frequently affected than men. Fracture (45 %), sprains (18 %), and surgery (12 %) are the most common initial causes. Spontaneous CRPS-like presenting with a similar clinical picture may occur in less than 10 % of cases.

40.5.3 Diagnosis

The diagnosis of CRPS is challenging because of the lack of gold standard procedures to confirm the clinical suspicion. Medical history and physical examination represent the only diagnostic criteria. The International Association for the Study of Pain has endorsed the Orlando criteria and the modified version known as the "Budapest criteria" [26] that includes motor features of the syndrome and has been validated. According to the "Budapest criteria," the diagnosis is based on symptoms and signs grouped into four distinct categories (Table 40.1).

Three stages of the CRPS are recognized. Stage 1 (acute phase) is characterized by pain, swelling, warming, and redness of the extremity. In stage 2 (dystrophic phase), the extremity becomes cool and cyanotic and shows trophic changes of hairs and nails, osteoporosis, stiffness, and muscle weakness. Stage 3 (atrophic phase) occurs when atrophy of bones, muscles, and skin become irreversible.

Three-phase bone scintigraphy can support the diagnosis providing evidence of typical bone changes. CRPS requires a differential diagnosis with neuropathic pain syndromes, vascular diseases, inflammatory and myofascial disorders, and psychiatric diseases.

Table 40.1 The "Budapest criteria" for the diagnosis of CRPS

1	**Continuing pain, which is disproportionate to any inciting event**
2	At least one symptom in three (clinical diagnostic criteria) or four (research diagnostic criteria) of the following categories: (a) Sensory: hyperesthesia or allodynia (b) Vasomotor: temperature asymmetry, skin color changes, or skin color asymmetry (c) Sudomotor or edema: edema, sweating changes, or sweating asymmetry (d) Motor or trophic: decreased range of motion, motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin)
3	At least one sign at the time of diagnosis in two or more of the following categories: (a) Sensory: hyperalgesia (to pinprick) or allodynia (to light touch, deep somatic pressure, or joint movement) (b) Vasomotor: temperature asymmetry, skin color changes or asymmetry (c) Sudomotor or edema: edema, sweating changes, or sweating asymmetry (d) Motor or trophic: decreased range of motion, or motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin)
4	**No other diagnosis better explains the signs and symptoms**

40.5.4 Treatments and Prognosis

Bisphosphonates and physical therapy to inhibit bone reabsorption, antiepileptic, antidepressant and opioids to control pain, and interventional therapies including nerve blockade, sympathetic (stellate ganglion) block, and sympathectomy have been reported to provide beneficial effects in patients. However, the management of CRPS requires a multidisciplinary approach including also psychological (pain coping skills, relaxation, and biofeedback) and rehabilitation treatments.

The incidence of severe complications of stellate ganglion block (e.g., bupivacaine, botulin toxin), mostly caused by inadvertent injection of the subarachnoid space, arteria vertebralis, or thoracic pleural cavity, has been estimated in 1.7/1,000 patients. Horner's syndrome and hoarseness caused by spreading of the anesthetic drug along the sympathetic cervical trunks or laryngeus recurrens nerve can occur.

Table 40.2 Factors influencing the prognosis of CRPS

Prognostic factors in CRPS	
Predictors of poor outcome	Predictors of good outcome
Longer pain duration	Fracture as trigger event
Intense pain	Absence of sensory symptoms
Delayed treatments	Presence of swelling
Younger age	Warm limb in early stages
Poorer grip strength and mobility	Early onset after tissue injury

Follow-up studies demonstrated that CRPS can have a highly variable course. Some patients experience a brief syndrome resolving in 6–12 months with minimal sequelae (weakness and stiffness), whereas others complain of long-lasting symptoms with chronic pain. Peripheral autonomic symptoms (vasomotor and sudomotor changes) most commonly recover in early stages, whereas skin trophic changes and motor symptoms (weakness, stiffness, dystonia) can persist also over years. Table 40.2 reports the prognostic factors of CRPS.

The recovery rate of CRPS was reported to range from 74 % in the first year to 36 % within 6 years. Severe CRPS outcome was reported to be rare, although most patients can experience persistent impairments at 2 or more years since onset. In a case series of 102 patients assessed at 5.8 years (range: 2.1–10.8) since onset, 16 % complained of progressive CRPS and 31 % could not work. Poorest outcome is associated with upper extremity involvement, trigger other than a fracture, and cold CRPS [27].

40.6 Phantom Pain

40.6.1 Definition

Phantom pain is a complex of sensation related to the removal of a part of the body. This phenomenon typically occurs after a limb amputation, but may also develop after radical surgery of other parts of the body, such as tongue, eyes, penis, or breast, after nerve or brachial plexus avulsion or spinal cord injury [28]. It has been described in about 20 % of children with congenital limb aplasia.

The pathophysiology of phantom limb remains unclear [29]. Central and peripheral mechanisms [28, 30] have been suggested to be determinant for the development of the disorder, which occurs in the majority of patients after an amputation and encompasses a wide range of symptoms.

40.6.2 Clinical Features

About 70 % of patients can experience phantom pain (e.g., shooting, stabbing, squeezing, or burning) immediately after the amputation, whereas 84 % of patients experience phantom sensations, namely, sensory illusions of the removed limb in the form of cold or warm feelings, itch, or tingling. These are part of the large spectrum of symptoms, which includes kinetic (movement) and kinesthetic (positional orientation) sensations. Patients can experience phantom movement (often referred to as painful spasm) and some are able to move the phantom at will. The phantom limb can assume unnatural positions in the space, such as outstretch in front, behind, or sideways. Telescoping is another perception reported as the phantom limb seems shortened and it feels like only the digits remain on the stump.

40.6.3 Therapy

Treatment of phantom pain is based on a multidisciplinary approach including neuropathic pain drugs (antidepressants, anticonvulsant, and opioids), physical therapies (acupuncture, ultrasound, TENS, motor, cortex, and spinal cord stimulation), rehabilitation programs, and, in a very limited number of critical patients, surgical treatments (revision of the stump, dorsal column tractotomy, dorsal root entry zone lesions) [31].

40.6.4 Prognosis

Phantom limb pain can spontaneously improve or resolve, but it persists over 2 years in 60 % of patients and is referred as severe in 0.5–5 %.

40.7 Painful Neuroma

40.7.1 Definition

The abnormal growth of Schwann cells and nerve fibers that can occur after a peripheral nerve injury is known as traumatic neuroma. It represents the ineffective attempt of regeneration and can develop in any nerve. Typical examples are Morton's neuroma (usually affecting the common digital nerve in the third planter space) or amputation neuroma (involving the distal stump of the truncated nerve). Pain has the features of neuropathic pain and the efficacy of the pharmacological treatments is often poor [32].

40.7.2 Treatments and Prognosis

Neuroma formation should be prevented in the case of predetermined surgical nerve injury (e.g., amputation) or surgical revision. Surgical approaches include relocating the nerve stump into an environment (such as bone, muscle, or vein) far from the original injury site and protecting the nerve from further injuries. In these cases, success rate with partial pain relief is 50–60 % [33].

40.8 Central Post-Stroke Pain

40.8.1 Definition

Central post-stroke pain (CPSP) is a condition arising as a consequence of a cerebrovascular disease. In the past, this condition was known as "Dejerine–Roussy syndrome" and strictly related to a thalamic stroke. The definition of CPSP has been currently extended and includes the whole somatosensory pathway as a possible site of injury.

40.8.2 Clinical Features

CPSP shows a neuroanatomic distribution that corresponds to the damaged central nervous system (CNS) area. It should not be confused with other common post-stroke pain syndromes, such

as shoulder pain, headache, or painful spasticity. The estimated prevalence of CPSP varies between 11 and 55 %, a wide range likely due to the lack of well-defined diagnostic criteria. Most commonly, CPSP occurs a few months after the CNS injury, although it can develop either immediately after the cerebrovascular event or years later.

40.8.3 Treatments and Prognosis

CPSP is difficult to treat and has a poor outcome.

Pharmacological treatments have limited efficacy despite multi-drug therapy (e.g., antidepressants, anticonvulsant, and opioids).

Neurostimulation targeting the sensory thalamus has shown a success rate of 45–50 % at 1-year follow-up [34]. The factors predisposing to the development of central pain after stroke are still unknown. A recent study found that patients with a lesion in the posterior and lateral thalamus have an increased risk to develop CPSP than those with anterior-medial lesions [35].

40.9 Postherpetic Neuralgia (PHN)

Key Facts

- **Terminology and definitions** – Pain in the territory of a cranial nerve or dermatome previously affected by Herpes Zoster infection, lasting >3 months after rash onset.
- **Clinical features** – Spontaneous (burning, stabbing, paroxysmal, itching) and evoked (light touch and pressure allodynia) neuropathic pain; possible motor involvement with waste and weakness. Facial weakness, corneal damage, vertigo and ipsilateral hearing loss, tinnitus may be present, according to Zoster localization.
- **Diagnosis** – Based on clinical and anamnestic information. No laboratory test is necessary.
- **Top Differential Diagnoses** – Herpes simplex virus, impetigo, candidiasis, contact dermatitis, insect bites, autoimmune blistering disease, dermatitis herpetiformis, drug eruptions.
- **Principles of treatment** – Tricyclic antidepressants, gabapentinoids, and topical lidocaine are first-line treatments.
- **Prognosis** – Pain can recover within 3 months from rash onset in most patients <50 years. PHN develop in 5 % of patients <60 years, 10 % of patients between 60 and 70, and in 20 % of patients aged 70 years or older. About 3 % of patients can experience PHN after 1 year. Live attenuated vaccine can reduce significantly the risk incidence of both HZ and PHN.

40.9.1 Definition

Postherpetic neuralgia (PHN) is the most common complication of Herpes Zoster (HZ) infection and is defined as pain in the territory of a cranial nerve or dermatome lasting more than 3 months after skin rash onset.

40.9.2 Epidemiology

The overall incidence of HZ infection ranges between 1.2 and 3.4 per 1,000 persons per years. Its frequency increased with aging from 2 cases per 1,000 persons under 50 years to 10 cases per 1,000 between 70 and 80 years. About 50 % of individuals who reach age 85 years may have had at least one episode of Herpes Zoster. Elderly and immunocompromised patients are at higher risk. PHN shows a similar age-related increase of incidence, from 5 % in subjects younger than 60 years to 10 % in those aged 60–69 years and up to 20 % in those aged 80 years or older [36].

40.9.3 Clinical Features

HZ infections are clinically characterized by three phases: pre-vesicular, acute eruptive, and chronic. The distribution of the shingles is dis-

tinctive. HZ is typically unilateral, does not cross the midline, and is usually localized to a single dermatome, though adjacent dermatomes can be involved in 20 % of cases. The most common sites are the thoracic nerves and the ophthalmic branch of the trigeminal nerve. Ophthalmic HZ represents 10–20 % of all cases and can lead to keratitis, corneal scarring, and vision loss. An early sign is the appearance of vesicles on the tip, side, or root of the nose (Hutchinson sign). HZ involving the second and third branches of the trigeminal nerve may cause symptoms and lesions in the mouth, ears, pharynx, or larynx. HZ of the fifth and eighth cranial nerves (Ramsay Hunt syndrome) can cause facial paralysis, tinnitus, vertigo, and deafness.

Patients affected by HZ can experience early sensory disturbances, frequently referred as localized burning pain or itching, since the pre-vesicular phase. After an average of 48 h, the acute eruptive phase occurs, often accompanied by more severe painful symptoms (e.g., aching, burning, stabbing, itching) in the affected area. Light touch allodynia (e.g., clothing brush, shower water) and pressure (e.g., lean back in a chair) is frequent and interferes with daily activities and sleep. Some patients can show autonomic changes including increased sweating, redness, swelling, and skin temperature changes in affected area. Muscle wasting and weakness can occur, causing abdominal pseudo-herniation or other motor defects reflecting the involvement of motor nerves.

40.9.4 Diagnosis

PHN is diagnosed based on the history of neuropathic pain persisting more than 3 months after shingles have healed. HZ infection is diagnosed on clinical ground by the evidence of prodromal pain and distinctive distribution of shingles.

Detection of viral DNA is the most reliable and quick diagnostic test, allowing results within a few hours. Vesicles contain a high concentration of virus that can be spread by contact and airborne route. HZ is contagious after the rash appears and until the lesions crust.

40.9.5 Treatment

Early diagnosis and treatment of HZ infection can reduce acute symptoms and may reduce the risk to develop PHN.

Topical medications and oral analgesics are effective to achieve pain relief in PHN. Tricyclic antidepressants (amitriptyline, nortriptyline) and gabapentinoids are recommended as first-line treatment.

Lidocaine 5 % plasters (once daily for up to 12 h within a 24 h period; subsequent plaster-free interval must be at least 12 h) may be considered first-line in the elderly, especially if there are concerns regarding the side effects of oral medications.

Opioids (e.g., tramadol, oxycodone), capsaicin 0.075 % cream, and capsaicin 8 % patch are recommended as second choice [37].

40.9.6 Prognosis

The risk to develop PHN increases with aging. The chance is higher in immunocompromised subjects and when HZ infection involves the ophthalmic branch of the trigeminal nerve and the brachial plexus. Lumbar and sacral localization has a lower risk of PHN. Severity of rash and severe prodromal sensory disturbances are also risk factors for PHN.

Overall, the prognosis is good. Only 3 % of patients older than 60 years complain of chronic PHN at 1 year. Live attenuated vaccine can reduce the incidence of HZ by 51 % and of PHN by 66 %, and is recommended in subjects older than 60 years [38].

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