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section 24 Neurological disorders 5956 Nyholm D, et al. (2003). Optimising levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets. *Clin Neuropharmacol*, 26, 156–63. Olanow CW, Watts RL, Koller WC (2001). An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. *Neurology*, 56 (11 Suppl 5), S1–88. Olanow W, Schapira AH, Rascol O (2000). Continuous dopamine- receptor stimulation in early Parkinson's disease. *Trends Neurosci*, 23, S117–26. Parkinson Study Group (2002). Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. *JAMA*, 287, 1653–61. Rascol O, et al. (2000). A five year study of the incidence of dyskinesias in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med*, 342, 1484–91. Rascol O, et al. (2002). Treatment interventions for Parkinson's disease: an evidence-based assessment. *Lancet*, 359, 1589–98. Stern MB, et al. (1989). Magnetic resonance imaging in Parkinson's disease and parkinsonian syndromes. *Neurology*, 39, 1524. van de Vijver RAC, et al. (2001). Estimation of incidence and prevalence of Parkinson's disease in the elderly using pharmacy records. *Pharmacoepidemiol Drug Safety*, 10, 549–54. Zhang Z, Roman G (1993). Worldwide occurrence of Parkinson's disease: an updated review. *Neuroepidemiology*, 12, 195–208. 24.7.3 Movement disorders other than Parkinson's disease Bettina Balint and Kailash Bhatia ESSENTIALS Hyperkinetic movement disorders are characterized by involuntary (and excessive) movements. The five main forms are chorea, tics, myoclonus, dystonia, and tremor, which can sometimes occur in combination. Some movement disorders are defined by their paroxysmal occurrence (paroxysmal movement disorders) or by their presence only during sleep, and there are other conditions that lie outside the conventional

list but are part of the spectrum of movement disorders, for example, stiff person syndrome. It is important to remember that drugs can cause a variety of movement disorders, including some very distinct presentations, and also that all organic movement disorders can be mimicked by so-called psychogenic or functional movement disorders. It is important not to miss treatable disorders (e.g. Wilson's disease, dopa-responsive dystonia, or some of the immune-mediated disorders), but in most cases treatment is symptomatic, both of motor and nonmotor (usually neuropsychiatric) features, which may significantly contribute to poorer quality of life. Most of the recent advances in this field are due to the discovery of new genes. The indications and application of deep brain stimulation has become much wider, with beneficial results not only in Parkinson's disease but also dystonia and some tremor disorders, and even Tourette syndrome.

Particular movement disorders

Chorea Inherited choreiform disorders—most are autosomal dominant, and divisible into those with onset in adulthood or childhood. Huntington's disease is a classic form of later onset, autosomal-dominant chorea often associated with dementia and psychiatric disturbance, whereas autosomal-dominant 'benign hereditary chorea' has very early onset with a more benign prognosis. Recessive forms of chorea usually have early onset and are generally associated with a variety of other neurological or systemic signs. Acquired chorea—possible aetiologies include drugs, immune-mediated, metabolic, infectious, and structural causes. The archetypical autoimmune chorea in children is Sydenham's chorea, but anti-N-methyl-D-aspartate receptor encephalitis is another important cause. Adult autoimmune chorea can be seen in a paraneoplastic disease and also in the context of systemic autoimmunity (e.g. anti phospholipid syndrome or systemic lupus erythematosus).

Dystonia Dystonia as sole sign is seen in a group of disorders (previously termed primary dystonia) which can be either idiopathic or genetic. Presentation follows a typical pattern with regard age of onset and body distribution, such as young onset generalized dystonia or adult onset focal dystonia (writer's cramp and craniocervical dystonia). Dystonia combined with other signs can be seen in various conditions, for example, dystonia combined with parkinsonism in dopa-responsive dystonia (including Segawa's disease), young onset Parkinson's disease, and Wilson's disease.

Myoclonus Myoclonus is characterized by very brief, shock-like, involuntary movements that can be positive, caused by sudden muscle contraction, or negative, due to a sudden lack of muscle tone (e.g. asterixis). Causes include metabolic, toxic, infectious, and autoimmune conditions. Symptomatic treatment is with agents such as clonazepam, valproate, levetiracetam, piracetam, and primidone, often in combination.

Tremor Tremor may be a sole and defining symptom (essential tremor) or be part of a syndrome (e.g. dystonic tremor or parkinsonian tremor). Treatment of tremor is purely symptomatic. Focal tremors (e.g. of head, jaw, voice) often show an excellent response to botulinum toxin injections. Tremor of the limbs often requires medical therapy: agents used include propranolol, clonazepam, primidone, topiramate, and gabapentin. Deep brain stimulation is considered for severe and disabling tremors, and focused ultrasound may be employed in the future.

Tics Tics mostly occur as primary disorders without any associated neurological disease. Presentation ranges from minor tics of self-limiting occurrence during childhood, which occur in up to 15% of school-age children (boys more than girls), and persistent tic disorders like Tourette syndrome, which can result in significant

24.7.3 Movement disorders other than Parkinson's disease 5957 physical and social disability. More rarely, tics can occur secondarily to neurodegenerative disease, in developmental disorders, as part of the spectrum of paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, or due to structural brain damage. Some drugs (e.g. amphetamines), are

associated with (re-) occurrence of tics. Other movement disorders These include restless legs syndrome and other sleep movement disorders, stiff person syndrome and related disorders, paroxysmal dyskinesias, drug-induced movement disorders, psychogenic movement disorders, and the interphase of movement disorders and peripheral nerve disorders like hemifacial spasm and myokymia. Introduction Movement disorders remains a subspecialty wherein the observed clinical phenomenology is of paramount importance and guides further investigations to find the right diagnosis. Here we outline the different clinical forms of hyperkinetic movement disorders and discuss the different diseases in the context of the main movement disorder presentations. Hyperkinetic movement disorders or dyskinesias are characterized by involuntary (and excessive) movements. The five main forms of dyskinesias include chorea, tics, myoclonus, dystonia, and tremor. In contrast to dyskinesias, hypokinetic disorders are defined by a poverty of movement such as in parkinsonian disorders. However, sometimes there can be a combination of different movement disorders. Some movement disorders are defined by their paroxysmal occurrence (paroxysmal movement disorders), or by their presence only during sleep such as rapid eye-movement (REM) sleep behaviour disorder (RBD), and periodic limb movements in sleep. In addition, there are still other conditions, for example, stiff person syndrome, which lie outside the conventional list of dyskinesias but are part of the spectrum of movement disorders. Also included here are miscellaneous movement disorders, such as hemifacial spasm, myokymia, and myorhythmia. It is important to remember that drugs can cause a variety of movement disorders, including some very distinct presentations, and this will be covered separately. Lastly, all organic movement disorders can be mimicked by so-called psychogenic or functional movement disorders, which will be discussed last. Treatment is often only symptomatic as there are mostly no cures. It is therefore important not to miss treatable disorders, such as Wilson's disease, dopa-responsive dystonia, or some of the immune-mediated disorders, but also rarer entities like biotin responsive encephalopathy or glucose transporter 1 deficiency. Furthermore, apart from the movement disorder aspect, it is important to recognize and treat certain nonmotor (usually neuropsychiatric) features, which may significantly contribute to poorer quality of life. Most of the recent advances in this field are due to the discovery of new genes, which start paving the way for the first genetic treatment trials, as in Huntington's disease. The indications and applications of deep brain stimulation have become much wider with beneficial results not only in Parkinson's disease, but also dystonia and some tremor disorders, and even Tourette syndrome. In the following section we will discuss each of the major forms of hyperkinetic movement disorders individually. Chorea Chorea is characterized by brief, irregular, purposeless movements that unpredictably flit from one body part to another and lend the patients a fidgety, restless appearance (see Video 24.7.3.1). Key questions in the approach to a patient with chorea are tempo and age of onset, family history, drug history, and distribution. For example, involvement of just one side (hemichorea) indicates a contralateral structural lesion. Ballism is a more severe form of chorea and often due to vascular lesions of the contralateral subthalamic nucleus (see Video 24.7.3.2). Chorea as the sole or main feature can underlie several different aetiologies, which may be broadly divided into inherited and acquired causes (for an overview see Table 24.7.3.1).

Table 24.7.3.1 Overview of the main causes of chorea classified by aetiology

Inherited	Autosomal dominant	Autosomal recessive	X-linked recessive
Adulthood onset	Huntington's disease C9ORF72 Junctophilin-3 Spinocerebellar ataxia 17, 1, 2, 3 DRPLA Prion disease Neuroferritinopathy Aceruloplasmaemia	Childhood onset Benign hereditary chorea (TITF-1) ADCY5 PDE10A Ataxia teleangiectasia Ataxia with oculomotor apraxia type 1, 2 and 4 Friedreich's ataxia Neuroacanthocytosis Wilson's disease Aminoacidurias Niemann-Pick C	X-linked recessive Lesch-Nyhan syndrome
Acquired	Autoimmune		

Childhood onset Sydenham's/PANDAS NMDAR antibody encephalitis Adulthood onset
Paraneoplastic disease (particularly related
to CRMP5 and Hu-antibodies) (continued)

section 24 Neurological disorders 5958 Inherited chorea The bulk of inherited choreiform disorders are autosomal dominant. These can be further subdivided into those with onset in adulthood or childhood. Huntington's disease is a classic form of later onset, autosomal-dominant chorea often associated with additional features such as dementia. On the other hand, autosomal-dominant 'benign hereditary chorea' has a very early onset with chorea as the main feature and with a more benign prognosis. Recessive forms of chorea as shown in Table 24.7.3.1 usually also have early onset but, generally, a variety of other neurological or systemic signs are associated with these syndromes.

Huntington's disease Huntington's disease (HD) is an autosomal-dominant neurodegenerative disorder with chorea, dementia, and psychiatric disturbance as the main features. It was first described by George Huntington in 1872 and proved to be the most frequent inherited cause of chorea, with a prevalence of 4–10/100 000 in western European populations.

Aetiology The underlying genetic defect is a triplet (CAG) repeat expansion, encoding polyglutamine in the huntingtin gene on chromosome 4p16.3. The mutant gene product forms aggregates in cells that lead to cell death, and neuropathologically to atrophy mainly of the cortex and caudate, more than the putamen. The CAG repeat ranges normally between 10–28 copies, but is expanded to a range of 36 and more in patients with HD. The number of CAG repeats correlates also with penetrance and phenotype. 40 or more CAG repeats are fully penetrant, whereas there is a borderline repeat range between 36 and 39 repeats with reduced penetrance. Usually, the higher the number of repeats, the earlier the presentation. There is a tendency for expansion of the triplet repeat during transmission, a phenomenon called anticipation, particularly if the disease is inherited through the father. This is explained by meiotic instability, which increases the CAG repeat number and is greater in spermatogenesis than in oogenesis.

Symptoms The disease usually manifests in the fourth decade, but age at onset can vary from adolescence (<18 years, Westphal variant with parkinsonism rather than chorea) to milder presentations late in life (often misdiagnosed as 'senile chorea'). Eye movement abnormalities often appear early and comprise difficulty with initiation, or slowness, of saccades and gaze distractibility. The latter can be considered part of motor impairment, which is also reflected in the difficulty of maintaining postures, for example, tongue protrusion ('chameleon tongue'). Patients may also feature hyperreflexia or 'hung up' tendon jerks (a tonic, slow response after the classical stretch reflex). Of note, the motor symptoms may change over the disease course, being initially most frequently chorea, and changing to dystonia and akinetic-rigid parkinsonism, with dysarthria and dysphagia in the very last stages. Other typical, nonmotor accompaniments are prominent neuropsychiatric disturbance, mainly depression and anxiety. The rate of suicides is much higher than in the general population. Cognitive problems often appear later, and encompass poor planning and judgement, lack of concentration and attention, and memory loss. Behavioural disturbance may be reflected in impulsivity or psychomotor slowing with apathy. It appears that the weight loss in HD is a symptom in its own right due to metabolic disturbance.

Diagnosis Brain imaging may give a diagnostic clue as it will often show caudate atrophy with ventricular dilatation. The diagnosis is made by genetic testing, which should be considered after proper genetic counselling. HD is a devastating disease which often has been passed on prior to development of any symptoms.

Important aspects to NMDAR antibody encephalitis Antiphospholipid syndrome Vasculitis Coeliac disease Systemic Lupus erythematosus Neurobehçet Drug induced L-dopa (L-dopa induced

dyskinesia in Parkinson's disease) Dopamine receptor blockers (tardive dyskinesia) Anticholinergics (e.g. trihexyphenidyl) Oral contraceptives Calcium channel blockers Anticonvulsants (e.g. phenytoin) Thyroxine Benzodiazepines Monoamine oxidase inhibitors Tricyclic antidepressants (e.g. amitriptyline) Digoxin Stimulants Alcohol withdrawal Metabolic abnormality Thyroid Parathyroid Glucose Sodium Calcium Magnesium Structural lesions Stroke Abscess Tumour Demyelination Infectious HIV Prion disease Other Polycythaemia rubra vera NMDAR, N-methyl-d-aspartate receptor; PANDAS, paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections; HIV, human immunodeficiency virus. Table 24.7.3.1 Continued

24.7.3 Movement disorders other than Parkinson's disease 5959 discuss beyond the nature of the disease itself are the possible test results (particularly the indeterminate range) and further ramifications with respect to mortgage and health and life insurance, as well as implications for other family members. Several other dominantly inherited conditions, so-called 'Huntington lookalikes' can mimic HD (Table 24.7.3.1). Among those, C9ORF72 mutations are probably the most frequent cause in Caucasian populations, whereas junctophilin-3 mutations are often found in those of African origin and DRPLA in the Japanese population. Treatment There is no therapy that can cure or slow the progression of HD, although in 2015, the first human trial of gene silencing with administration of an antisense oligonucleotide started. To date, however, treatment remains symptomatic and requires multidisciplinary management. An early, empathic discussion of the preferences regarding the long term and the living will is therefore crucial. It is often the psychiatric symptoms which cause major distress and which primarily need to be treated (e.g. depression with selective serotonergic reuptake inhibitors (SSRIs), anxiety with benzodiazepines, psychosis with atypical neuroleptics). If treatment of chorea should be required, tetrabenazine and dopamine receptor blocking agents are acceptable options. However, tetrabenazine is to be used with caution as it can aggravate depression. Other measures comprise weight maintenance with a high calorie diet, as well as speech and language therapy. Benign hereditary chorea The term 'benign hereditary chorea' was initially coined to describe autosomal-dominantly inherited chorea with onset in infancy. Patients often also have disorders of the thyroid or the lungs, as the underlying gene, TITF-1, plays an important role in the organogenesis of brain, thyroid, and lung. More recently, mutations in other genes like ADCY5 and PDE10A have emerged as another cause of autosomal-dominant chorea with childhood onset. Acquired chorea The possible aetiologies of acquired chorea are manifold and include drugs, immune-mediated, metabolic, infectious, and structural causes (Table 24.7.3.1). It is important to keep in mind treatable causes when approaching the differential diagnosis. In this context, we will focus here on autoimmune chorea. Onset age is a crucial determinant in this regard. Autoimmune chorea The archetypical autoimmune chorea in children is Sydenham's chorea. Anti-NMDAR encephalitis is an increasingly recognized entity affecting all age groups. Adult autoimmune chorea can be seen in a paraneoplastic disease (mostly related to lung cancer, with CRMP5- and Hu-antibodies), but also in the context of systemic autoimmunity (e.g. antiphospholipid syndrome or systemic lupus erythematosus). Here, the underlying pathophysiology is however poorly understood. Sydenham's chorea Thomas Sydenham (1624–1689), who lent his name to the syndrome, was an English physician who described chorea affecting children and adolescents. Thereafter, its association to group A streptococcal infections and rheumatic fever was recognized. Affected children usually present with acute to subacute onset of chorea or hemichorea, often accompanied by behavioural disturbance. As in many other autoimmune disorders, females are more commonly affected than males, and may be affected by recurrence of symptoms, particularly when taking

oral contraceptives or during pregnancy. Recurrences may also occur spontaneously, but most patients experience complete remission of symptoms within 5–15 weeks. Only very few patients suffer from persistent chorea. The pathophysiology remains unclear, although a cross-reaction ('molecular mimicry') between immunity directed against the streptococcus and the basal ganglia is hypothesized. Antistreptolysin titres can support the diagnosis, whereas the previously propagated antibasal ganglia antibodies are nowadays considered of little value. Treatment consists of acute therapy with oral penicillin and prophylaxis with monthly benzathine penicillin injections for five years or until reaching adulthood. Anti-NMDAR encephalitis Encephalitis with N-methyl-d-aspartate receptor (NMDAR) antibodies can mimic Sydenham's chorea as children often present with chorea and only mild neuropsychiatric features. In children, it can be 'idiopathic' or occur triggered by herpes virus encephalitis and lead to 'choreatic relapses'. Anti-NMDAR encephalitis can also affect adult patients and is, in nearly half of the female patients, a paraneoplastic phenomenon associated with ovarian teratomas. Classically it presents with an acute onset of neuropsychiatric disturbance with subsequent development of movement disorders, epilepsy, cognitive impairment, loss of consciousness, dysautonomia, and central hypoventilation. Treatment consists of immunosuppression and tumour removal where appropriate. Timely diagnosis, which can be confirmed by detection of the antibodies in serum (and more specifically, in the cerebrospinal fluid) is crucial, as the outcome is improved the earlier treatment is initiated and the condition can be lethal if not recognized. Dystonia Dystonia is defined as 'sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both'. Dystonic movements which become primarily evident on action are often patterned and twisting. Tremor can be a feature. Another characteristic feature is the 'geste antagoniste' or sensory trick, whereby dystonia movements can be alleviated by a touch of the affected body part. For example, touching the head or face in cervical dystonia can help reduce the torticollis. Dystonia may be a clinical feature in the presentation of several conditions in which dystonia is present as the sole symptom or associated with other clinical features. Hence one must use the clinical characteristics such as age at onset, body distribution, temporal pattern, associated feature as markers to establish the aetiology, namely whether it is idiopathic or due to a hereditary or acquired cause. Traditionally, we used to classify dystonia as either primary dystonia or secondary dystonia. In the primary form dystonia is the sole feature (apart from tremor) and can be either idiopathic or due to a genetic cause. In contrast, where dystonia was due to secondary

section 24 Neurological disorders 5960 acquired or hereditary/degenerative causes, additional neurological or other features were often present and dystonia was considered as part of a dystonia-plus syndrome. A new classification now defines dystonia on a clinical and an aetiological axis. In this context, dystonia is considered clinically as 'isolated' when there are no other associated features or 'combined' when there are. This definition largely overlaps with the previous classification of primary generally 'isolated dystonia' and 'combined dystonia' in which it is part of a syndrome due to different aetiologies which come into the differential diagnosis. The recent advances in the field of dystonia comprise the discovery of several new genes (Table 24.7.3.2 and 24.7.3.4), and the recognition of so-called nonmotor features, such as depression, which significantly contribute to the burden of the disease and impaired quality of life. Primary dystonia (isolated dystonia) Primary dystonia can be idiopathic or genetic (Table 24.7.3.2). Both forms present insidiously and follow a characteristic pattern with regard anatomical distribution in relation to age at onset. Discrepancy from this pattern, among other red flags (Table 24.7.3.3), cautions against primary dystonia and may suggest secondary or symptomatic dystonia. Young

onset generalized dystonia (primary torsion dystonia) Manifestation in childhood or adolescence usually involves onset in the legs with subsequent generalization (see Fig. 24.7.3.1). Thus, first symptoms typically are in-turning of the feet and pigeon-toed walking before, in most of the cases, over the course of months to years, dystonia spreads to other body parts. This phenotype was described by Oppenheim in 1911 as 'dystonia musculorum deformans' and subsequently called primary torsion dystonia. Later on, TOR1A (Torsin1A) gene mutations emerged as a frequent cause of Oppenheim's dystonia. TOR1A mutations (also labelled as DYT1) are autosomal-dominantly inherited, however with reduced (30–40%) penetrance. They account in primary, early-onset dystonia for c.80% of the cases in Ashkenazi Jewish populations, and up to 50% in non-Jewish populations. Another genetic form of young onset generalized dystonia is DYT6 due to mutations in the THAP1 (thanatos-associated protein) gene. It differs from DYT1 inasmuch the sites of onset are the upper limbs, or the craniocervical region with prominent laryngeal involvement. Adult onset focal dystonia (writer's cramp and craniocervical dystonia) Much more (9–12 times) frequent than young onset, generalized dystonia are, however, the focal variants with onset in middle or late adulthood, which only rarely have genetic underpinnings. Writer's cramp and other task-specific dystonias Writer's cramp usually manifests in the fourth decade as abnormal posturing when attempting to write. Patients may already have difficulty picking up or holding a pen. When writing, they hold the pen with excessive force and dystonic posture of the hand and forearm (see Fig. 24.7.3.1), and experience increasing difficulties as writing continues. In order to cope with this, patients may try a different way to hold the pen, or pens of different sizes, or even learn to write with the other hand. However, some patients may then develop writer's

Table 24.7.3.2 Identified genes in primary (isolated) dystonia

Gene (designation)	Mode of inheritance	Age of onset	Dystonia distribution	Clinical characteristics
DYT1 (TOR1A)	AD	Childhood	Generalized; rarely focal	Isolated dystonia starting in legs and spreading; sparing of larynx and neck; can be jerky
DYT2 (HPCA)	AR	Childhood—early adulthood	Generalized, segmental	Isolated dystonia Onset with limb dystonia, slow progression to generalized or segmental dystonia with predominant craniocervical involvement
DYT4 (TUBB4A)	AD	Adolescence—early adulthood	Focal, segmental, generalized	Isolated/combined rare cause of isolated dystonia, prominent laryngeal ('whispering dysphonia') and oromandibular involvement; TUBB4A mutations present more often as the complex HABC spectrum
DYT6 (THAP1)	AD	Adolescence—early adulthood	Generalized	

■ segmental Prominent laryngeal involvement; rostrocaudal gradient DYT23 (CIZ1)
 CIZ1 (DYT23) AD Adolescence—adulthood Focal (Tremulous) cervical dystonia; rare/awaiting confirmation DYT24 (ANO3)
 ANO3 (DYT24) AD Childhood—adulthood Focal, segmental Tremulous cervical dystonia; cranial, laryngeal, UL involvement; can present with isolated arm tremor, or as a myoclonus-dystonia DYT25 (GNAL)
 GNAL (DYT25) AD Childhood—adulthood Focal, segmental, rarely generalized Cervical dystonia; head or tremor; laryngeal dystonia; generalization in 10%; hyposmia in some cases DYT27 (COL6A3)
 COL6A3 (DYT27) AR Childhood—early adulthood Segmental Mainly affecting the upper body, predominant craniocervical involvement; neck or hand being mostly

the site of onset AD, autosomal dominant; AR, autosomal recessive.

Table 24.7.3.3 Red flags cautioning against a diagnosis of primary dystonia •

Unusual pattern with regard to age of onset and distribution • Sudden onset with rapid progression • History of perinatal birth injury • Developmental delay • Exposure to drugs (e.g. dopamine receptor blockers) • Presence of other neurological or systemic signs • Prominent bulbar involvement with tongue protrusion and dysphagia • Hemidystonia • Fixed dystonia

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cramp in the other hand, or develop dystonia which is not limited only to the task of writing itself, but hampers other activities such as using cutlery, brushing teeth, and so on. Other craft or occupational cramps may occur wherever repetitive, stereotyped movements are performed, and are described in piano players, typists, and hair-dressers among many others. Cervical dystonia Cervical dystonia is the most common form of dystonia with prevalence rates ranging from 89 up to 732 per 100 000. It affects mainly women in their fourth or fifth decade of life. The most frequent form is torticollis (head turning to one side), but variations such as laterocollis (tilt to the side), retrocollis (neck extension) and anterocollis (neck flexion), or mixed forms can occur. Cranial dystonia Dystonia affecting the face may present as blepharospasm (eye closing spasms), oromandibular dystonia, or a combination of these ('Meige syndrome'). Laryngeal or laryngopharyngeal dystonia ('spasmodic dysphonia') also figures among the cranial dystonias, which are again more frequent among women and mainly occur around the sixth decade. Treatment There are several options for the symptomatic treatment of dystonia, but there is no cure. These include a variety of drugs such as anticholinergics, benzodiazepines, gabaergic agents, and dopamine receptor blockers (as well as depleters such as tetrabenazine). Intramuscular botulinum toxin injections are the preferred treatment for focal dystonias and functional neurosurgery with deep brain stimulation, targeting the internal segment of the globus pallidus can be very effective, particularly in primary dystonia. Other surgical procedures, such as peripheral denervation of affected muscles in craniocervical dystonia or lesional brain surgery targeting the globus pallidus or thalamus have been largely abandoned due to the success and relative safety of deep brain stimulation. Ancillary treatments include physical and speech therapy, which are useful, whereas retraining strategies particularly for task-specific dystonias (e.g. musician's dystonia) have been tried, but are of uncertain value in the long term. Dystonia plus syndromes ('combined dystonia') When dystonia is combined with other movement disorders, it falls into the category of 'combined dystonia'. Besides, other neurological signs such as deafness, neuropathy, or eye movement disorders can give valuable clues to the diagnosis. In the following, we will discuss in more detail the syndromes of dystonia and parkinsonism, and dystonia and myoclonus, and provide a general overview of combined dystonias (Table 24.7.3.4). Dystonia and parkinsonism Dopa-responsive dystonia Several genetic enzymatic defects affecting the dopamine synthesis pathway can cause dopa-responsive dystonia. The archetypic form is Segawa's disease due to autosomal-dominantly inherited GCH1 mutations. GCH1 stands for guanidine triphosphate cyclohydrolase 1, a gene encoding the rate-limiting enzyme in the production of tetrahydrobiopterin, itself an essential cofactor in the dopamine synthesis. Its hallmark features are dystonia commencing in childhood or adolescence, mainly in the lower limbs, diurnal fluctuation of symptoms (increasing as the day progresses) and an exquisite response to small doses of levodopa (200–400 mg per day). Often patients also have

signs of parkinsonism and, sometimes, spasticity. There are, however, other autosomal recessive forms of childhood monoamine neurotransmitter disorders, which usually give rise to a more complex phenotype (e.g. with myoclonus and epilepsy) and have less treatment response. Examples include tyrosine hydroxylase deficiency or sepiapterin deficiency. Recognition of these entities is important for the treatment implications. Thus, every child with a phenotype of cerebral palsy and every person with young onset dys- tonia (<25 years) should have a trial of levodopa. A final diagnosis can be made by genetic testing, phenylalanine loading test, and cere- brospinal fluid analysis of pterins. Young onset Parkinson's disease Young onset Parkinson's disease (YOPD) can sometimes present with limb dystonia (often foot dystonia). It is an important differ- ential diagnosis to dopa-responsive dystonia. To avoid the priming effect of levodopa and subsequent dyskinesias and fluctuations, it is important to diagnose this condition, but avoid giving levodopa as a test dose when YOPD is suspected (as both dopa-responsive dystonia and also these patients respond well to levodopa). In this regard, presynaptic dopaminergic imaging is very valuable as a dopamine transporter single-photon emission CT (SPECT) scan (DAT scan) is generally normal in dopa-responsive dystonia. Wilson's disease Wilson's disease is another important, treatable cause of dystonia and parkinsonism. It is a comparatively rare (approximately 15–30/ 100 000 per year), autosomal recessive copper metabolism disorder that leads to copper deposition in liver, the central nervous system Fig. 24.7.3.1 The spectrum of primary dystonia: young onset generalized dystonia, writer's cramp, cervical dystonia with geste antagoniste, and blepharospasm.

section 24 Neurological disorders 5962 Table 24.7.3.4 Combined dystonia syndromes Dystonia and parkinsonism syndromes Parkinson's disease, particularly with young onset See text Atypical parkinsonism Corticobasal syndrome Multisystem atrophy Progressive supranuclear palsy See Chapter 24.7.2 Wilson's disease See text Neuronal brain iron accumulation syndromes Autosomal recessive forms: PANK2 mutations (formerly Hallervorden-Spatz disease) PLA2G6 mutations CP mutations (Aceruloplasminaemia) C9ORF12 mutations (mitochondrial membrane protein-associated neurodegeneration, MPAN) FA2H mutations (fatty acid hydroxylase-associated neurodegeneration) ATP13A2-mutations (Kufor-Rakeb disease) CoAsy mutations (CoA synthase associated neurodegeneration, CoPAN) Autosomal dominant forms: FTL mutations (Neuroferritinopathy) X-linked dominant WDR45 mutations (BPAN, β -propeller protein-associated neurodegeneration; formerly SENDA, static encephalopathy of childhood with neurodegeneration in adulthood) Group of genetic disorders characterized by brain iron accumulation with a variety of manifestations Prominent bulbar involvement and dystonic opisthotonus are red flags Rapid-onset dystonia-parkinsonism (ATP1A3 gene, AD, often de novo) Allelic disorder to 'alternating hemiplegia of childhood'; prominent bulbar symptoms of abrupt onset, often associated with triggering factors (stress, alcohol, exercise, hyperthermia and hypothermia, childbirth); not responsive to L-dopa X-linked dystonia-parkinsonism (DYT3; TAF1 mutations, XLR) Also called Lubag; adult onset dystonia-parkinsonism, most prevalent in Philippino males Early-onset dystonia-parkinsonism (DYT16; PRKRA, ar) Early onset of generalized dystonia, prominent oromandibular involvement, retrocollis and dystonic opisthotonus Dopa-responsive dystonias See text Dopamine transporter deficiency syndrome (SLC6A3, ar) infantile or juvenile onset dystonia-parkinsonism not responding to levodopa Huntington's disease See text Spinocerebellar ataxia (esp. SCA 3) See Chapter 27.7.4 on ataxia GM1 gangliosidosis Lysosomal storage disorder due to homozygous mutations of the GLB1 gene causing variable degrees of neurodegeneration Dystonia and

myoclonus syndromes Myoclonus-dystonia (DYT11; SCGE) See text ANO3 mutations (DYT24, AD) Childhood-adulthood onset tremulous cervical dystonia that can present as a myoclonus-dystonia KCTD17 mutations (DYT26, AD) Onset in the first or second decade of life with myoclonus of the upper limbs; dystonia develops later (mainly craniocervical, sometimes segmental with upper limb involvement, rarely generalized). TITF1 mutations (benign hereditary chorea) See text TH deficiency (DYT5b) See text Dystonia and ataxia syndromes Spinocerebellar ataxias See Chapter 27.7.4 on ataxia Ataxia telangiectasia Autosomal recessive disorder (ATM gene) causing a wide spectrum of movement disorders associated with oculomotor apraxia, telangiectasias, and immunodeficiency leading to liability to develop malignancies Ataxia with oculomotor apraxia type 1 and 2 Autosomal recessive disorders (aprataxin and senataxin mutations, respectively) which can mimic ataxia telangiectasia Friedreich's ataxia See Chapter 27.7.4 on ataxia Neuroacanthocytosis Group of disorders characterized by acanthocytes and progressive neurological decline Wilson's disease See text Dentatorubropallidoluysian atrophy Autosomal dominant condition (ATN1 gene) with a wide spectrum of manifestations (continued)

24.7.3 Movement disorders other than Parkinson's disease 5963 (mainly basal ganglia, cerebellum), cornea, and kidneys, thus pre- senting with a variety of symptoms. Two main forms of manifestation are recognized; the hepatic form with earlier onset in childhood, and a neurological form with onset usually in late childhood/early adolescence. However, late onset even at the age of 52 years has been reported and hence a high index of suspicion is warranted. Wilson's disease has manifold neurological manifestations. Dystonia and parkinsonism, cerebellar signs, chorea, myoclonus, or psychiatric disturbance have all been described. There is also a typical tremor associated with Wilson's disease resembling rubral tremor which is present at rest, worse on posture and most severe on action, and which has a characteristic 'wing-beating' proximal component. An important pathognomonic finding is the presence of corneal 'Kayser-Fleischer rings' consisting of red-brown pigmentation around the edge of the iris due to de- position of copper in the Descemet's membrane (see Fig. 24.7.3.2). These are best seen on slit-lamp examination. Similarly, sunflower cataracts due to a radiating, red-brown pattern of copper deposition in the lens can point to the diagnosis. Apart from cases with rapidly progressive liver failure, where liver transplant is the therapy of choice, the be-all and end-all of treat- ment in Wilson's is copper chelation therapy. The chelating agents, penicillamine and trientine, are the mainstay of treatment initiation and can also be used for the maintenance therapy, either after suc- cessful treatment initiation or in presymptomatic subjects. Zinc can also be used in the maintenance phase, but it inhibits only the re- sorption of copper and is a less powerful drug. Both patients and treating doctors need perseverance. Firstly, there can be a worsening of neurological symptoms soon after the initiation of therapy, par- ticularly with penicillamine. This, however, reverses either with a reduced dosage or continuation of therapy in most cases. Secondly, lifelong treatment is essential and needs to be continued even when patients are asymptomatic. Thus, continuous monitoring and maintaining compliance are key. The hallmark findings in the diagnostic work-up are low serum caeruloplasmin levels together with a raised 24-hour urinary copper excretion. However, as those tests are not always conclusive it is sometimes necessary to resort to a liver biopsy, where a copper con- tent greater than 250 micrograms/g dry weight of liver is considered diagnostic. Currently, genetic testing can be considered, but may be impractical as there are more than 600 mutations in the affected ATP7B gene, although there is some regional clustering of certain mutations. Brain MRI is normal in approximately 50% of the cases, but can show hyperintensities in the putamen, the pallidum, and the thalamus, or the typical 'face of the giant panda sign' due to

midbrain atrophy and high signal in the tegmentum in T2 weighted sequences (Fig. 24.7.3.3).

Myoclonus-dystonia The typical condition combining myoclonus and dystonia is due to epsilon sarcoglycan gene mutations and termed DYT11. The term myoclonus-dystonia is often used synonymously with DYT11, although there are other entities that can give rise to such a syndrome. DYT11 is an autosomal-dominantly inherited disorder with onset in infancy or early childhood. The brief myoclonic jerks ('lightening jerks') which affect mainly neck and arms often dominate the clinical picture, whereas dystonia of the neck and arms tends to be a comparatively minor feature. In fact, many cases of 'essential myoclonus' Multiple system atrophy See text

Niemann–Pick type C Autosomal recessive lysosomal storage disease (NPC1 mutations) with a wide spectrum of central nervous system symptoms (characteristic: vertical supranuclear gaze palsy) and hepatomegaly

GM2-gangliosidosis A group of autosomal recessive disorders caused by excessive accumulation of ganglioside GM2 and related glycolipids in the lysosomes; wide phenotypic spectrum

Dystonia and neuropathy syndromes Metachromatic leukodystrophy

Lysosomal storage disease with a wide spectrum of manifestations

Neuroacanthocytosis See above

Spinocerebellar ataxia See Chapter 27.7.4 on ataxia

GM2 gangliosidosis See above

Dystonia and deafness syndromes Mohr-Tranebjaerg syndrome (TIMM8A, x-linked recessive) Often associated with progressive blindness and dementia

Mitochondrial disorders Deafness, diabetes, or myopathy are characteristic findings in mitochondrial disorders, which can manifest with a wide spectrum of phenotypes

Woodhouse–Sakati syndrome (C2ORF37, AR) Hypogonadism, partial alopecia, diabetes mellitus, mental retardation

AD, autosomal dominant; AR, autosomal recessive; XLR, x-linked recessive. Table 24.7.3.4 Continued Fig. 24.7.3.2 Kayser–Fleischer corneal rings in Wilson's disease.

section 24 Neurological disorders 5964 have been found to be due to epsilon sarcoglycan gene mutations. The symptoms often show a dramatic response to small quantities of alcohol.

Psychiatric comorbidity (e.g. obsessive-compulsive behaviour, anxiety, or depression), is another well-recognized feature of the disease. However, several other genetic entities can manifest with a combination of myoclonus and dystonia, including mutations in ANO3 (DYT24), KCTD17 (DYT26), and TH (DYT5b) genes. In addition, patients with benign hereditary chorea, due to TITF-1 gene mutations, may develop a myoclonus-dystonia phenotype during the course of their disease.

Myoclonus Myoclonus is characterized by very brief, shock-like, involuntary movements (see Video 24.7.3.3); it can be positive, caused by sudden muscle contraction, or negative, due to a sudden lack of muscle tone (e.g. asterixis). There are various approaches to the classification of myoclonus, for example, clinically by distribution (focal, segmental, multifocal, generalized; proximal, distal) and inducing factors (spontaneous, on action, stimulus-sensitive or reflex myoclonus induced e.g. by sound or touch, orthostatic). Another approach takes into account the origin of myoclonus (cortical, sub-cortical/basal ganglia, brainstem, spinal, peripheral), which can be localized by electrophysiological investigations (see Box 24.7.3.1). Lastly, by aetiology, myoclonus can be divided into physiological, essential, epileptic, symptomatic, or psychogenic/functional. There is a multitude of disorders which can feature myoclonus, but the differential diagnosis can be narrowed down when taking into consideration age at onset, tempo of onset, precipitating factors including drugs and past medical history, and family history and associated features. Table 24.7.3.5 gives an overview of myoclonic disorders based on their phenomenology. The therapeutic approach naturally depends on the underlying aetiology and, in this regard, metabolic, toxic, infectious, and autoimmune causes deserve particular consideration. Several agents such as clonazepam, valproate, levetiracetam, piracetam, and primidone are

available for symptomatic treatment and, often, combination therapy is required. For example, in cortical myoclonus, the synergistic effects of valproate, clonazepam, and levetiracetam have proved beneficial. Isolated myoclonus See myoclonus-dystonia/DYT11.

Hereditary and acquired hyperekplexia and other startle syndromes Hyperekplexia is a form of brainstem myoclonus and best described as a pathological exaggeration of a normal startle response. Just as normal startle places the body in a defensive posture, it manifests with a stereotyped, generalized brisk response, mainly consisting of neck and trunk flexion, eye closure and facial grimacing, and shoulder elevation. In contrast to normal startle, however, it does neither habituate upon repeated stimulation nor attenuate with prewarning. Patients often also exhibit an uninhibited head retraction reflex, which can be elicited by tactile stimulation of the mantle area (e.g. a gentle touch of forehead, nose, lips, upper chest). Other features, apart from the brisk myoclonic jerks, are longer-lasting Fig. 24.7.3.3 Bilateral abnormal signal in the striatum and thalamus in Wilson's disease (left) and 'face of the giant panda' (right) on T2 weighted MRI sequences in Wilson's disease. Courtesy of Dr Annu Aggarwal.

Box 24.7.3.1 Electrophysiological investigations in myoclonus

- Polymyography (EMG): useful to establish the duration and distribution of jerks and to establish the presence of negative myoclonus or stimulus-sensitivity. Bursts of 50–75 ms or shorter are generally seen in cortical myoclonus, while longer bursts are seen in subcortical myoclonus such as in myoclonus-dystonia.
- Electroencephalography (EEG) and back-averaging: EEG per se is helpful to detect epileptic discharges. Back-averaging is a technique of averaging out EEG activity accompanying an EMG recording of various jerks to reveal time-locked cortical EEG discharges preceding individual myoclonic jerks (as seen in cortical myoclonus). A slow rising wave prior to psychogenic/functional jerks is called the Bereitschaftspotential (premovement potential).
- Somatosensory evoked potentials (SSEP): Giant SSEPs are an electrophysiological hallmark feature of cortical myoclonus.
- C-reflex: This is a long loop reflex mediated by the sensory-motor cortex. Enhanced C-reflexes are another characteristic of cortical myoclonus.

24.7.3 Movement disorders other than Parkinson's disease 5965 Table 24.7.3.5 Overview of myoclonic disorders based on their phenomenology

Disorder	Phenomenology	Aetiology	Notes
Isolated myoclonus	Hiccup, hypnic jerks, startle response	Physiological	Benign neonatal sleep myoclonus
Myoclonus	affects limbs, occurs exclusively during sleep, and stops on awakening; self-limiting and usually not present after 3 months of age	Essential myoclonus	Genetic: often epsilon sarcoglycan gene mutations/DYT11 (AD) Very brief ('lightening') jerks affecting mainly neck and arms; see text
Familial cortical myoclonus (also: benign adult onset familial myoclonic epilepsy)	Genetic: NOL3, ADRA2B, CNTN2, other mutations (AD) Also called 'cortical tremor', which is a misnomer, but highlights its resemblance with tremor; fine, shivering-like myoclonus affecting the distal limbs, mainly hands; rarely occurring without seizures; onset in 3rd or 4th decade; see text	Hereditary hyperekplexia	Genetic: mutations affecting the glycine receptor (GLRB, AR; GLRA1, AD, or AR) or glycine transporter (SCL6A5, AR, AD) Exaggerated startle response to touch or noise, present already at birth; usually decreasing throughout life; see text
Orthostatic myoclonus	Unknown Rare manifestation of autoimmune and neurodegenerative conditions with myoclonus of the legs occurring only while standing	Myoclonus with dystonia	Myoclonus-dystonia Genetic: DYT11 (SGCE mutations, AD); DYT15 (18p11, AD); DYT27 (KCDT17 mutations, AD) Mostly neck and arms affected, myoclonus may be the dominant feature; see text
Myoclonus with epilepsy	Benign myoclonic epilepsy of infancy Unknown (probably genetic)	Myoclonic jerks	involving mainly neck and arms, the consciousness remains usually preserved;

febrile convulsions but no other seizures associated; onset 6 months—3 years, male preponderance Juvenile myoclonic epilepsy Genetic: GABAA1 (AD) Onset around puberty, myoclonic jerks affecting mainly the arms and occurring typically on awakening; can be associated with generalized tonic-clonic seizures or absences Familial cortical myoclonus/ (also: benign adult onset familial myoclonic epilepsy) Genetic: heterogeneous (ADRA2B, CNTN2, NOL3, other loci; AD) Also called 'cortical tremor', which is a misnomer, but highlights its resemblance with tremor; fine, shivering-like myoclonus affecting the distal limbs, mainly hands; rarely occurring without seizures; onset in 3rd or 4th decade; see text West syndrome Various aetiologies, often symptomatic (tuberous sclerosis, perinatal hypoxia, congenital infections, malformations, craniocerebral injury) Childhood-onset epilepsy syndrome with severe encephalopathy Dravet syndrome Genetic: De novo mutations in SCN1A, GABRG2 Childhood-onset epilepsy syndrome with severe encephalopathy Lennox Gastaut syndrome Various aetiologies Childhood-onset epilepsy syndrome with severe encephalopathy Doose syndrome (myoclonic astatic epilepsy) Unknown Childhood-onset epilepsy syndrome with or without encephalopathy Epilepsia partialis continua Cortical lesion Characteristic syndrome of myoclonus affecting constantly one or adjacent body parts Myoclonus with ataxia ('Ramsay Hunt syndrome') • No or very mild cognitive impairment Unverricht-Lundborg disease/'baltic myoclonus' Genetic: CSTB (AR) onset between 6 to 15 yrs with stimulus-sensitive myoclonus and generalized tonic-clonic seizures; see text North Sea myoclonus Genetic: GOSR2 (AR) Onset around age 2 years with ataxia; myoclonus develops later, around age 6 years; other features include scoliosis and areflexia; see text Action myoclonus renal failure Genetic: SCARB2 (AR) Renal failure not an obligatory feature; onset usually in adolescence or early adulthood (continued)

section 24 Neurological disorders 5966 Phenomenology Disorder Aetiology Notes Progressive myoclonus

Epilepsy-ataxia syndrome Genetic: PRICKLE1 (AR) Onset between 5 to 10 years; can feature upgaze restriction Myoclonus epilepsy and ataxia due to potassium channel mutation (MEAK) Genetic: KCNC1 (AD) Age at onset 5–14 years; infrequent tonic-clonic seizures SCA14 Genetic: PRKCG (AD) Age at onset varies from early to late adulthood; other features may comprise spasticity and dystonia Coeliac disease Unknown (probably autoimmune) Gluten-sensitive enteropathy, usually manifesting with diarrhoea • With or without cognitive impairment Dentato-rubro-pallido-luysian atrophy (DRPLA) Genetic: ATN1 (AD) Age of onset varies from 1 to 62 years; similar heterogeneity in clinical presentation, but the Ramsay Hunt presentation starts usually before 20 yrs Mitochondrial disorders, e.g. myoclonic epilepsy with ragged-red fibres (MERRF) Genetic: MTTK, MTTL1, MTTH, MTTs1, MTTs2, MTTF (maternal) Short stature, deafness, myopathy • With cognitive impairment Lafora disease Genetic: EPM2A, NHLRC1 (AR) Onset in 2nd decade; generalized tonic-clonic seizures, and characteristic occipital seizures; death after 2–10 yrs; axillary skin biopsy shows pas-positive polyglucosan inclusion bodies; see text Neuronal ceroid lipofuscinosis Genetic: CLN1-14 (mostly AR; CLN4B AD) Visual disturbance, extrapyramidal symptoms, rapidly progressive psychomotor deterioration; see text Sialidoses Genetic: NEU1 (AR) Type 2 presents with visual disturbance, cherry red spot, skeletal dysplasia, and has a reduced life expectancy; type 1 is the more benign form where dementia is usually not a feature; see text Prion disease Genetic: PRNP (AD or sporadic) Myoclonus is diffuse, generalized, relatively rhythmic, often stimulus-sensitive, and can persist during sleep Niemann-Pick C Genetic: NPC1, NPC2 (AR) Hepatosplenomegaly, vertical supranuclear gaze palsy Gaucher Type III Genetic: GBA (AR) Hepatosplenomegaly, horizontal supranuclear gaze palsy GM2 gangliosidosis (Tay-Sachs disease,

Sandhoff's disease) Genetic: HexA, HexB, GM2A (AR) group of disorders caused by excessive accumulation of ganglioside GM2 and related glycolipids in the lysosomes Late infantile and juvenile forms feature myoclonus, epilepsy, ataxia, dementia, spasticity Myoclonus with opsoclonus Opsoclonus-myoclonus ataxia syndrome Autoimmune (+/- paraneoplastic; in children often associated with neuroblastoma) Opsoclonus (spontaneous, involuntary, multidirectional, 'chaotic' saccades) is the key feature; see text Myoclonus with parkinsonism/dementia Atypical parkinsonism syndromes • Multisystem atrophy (MSA) Neurodegeneration (α -synucleinopathy) small-amplitude myoclonus of the hands and/or fingers on posture: 'polyminimyoclonus' • Dementia with Lewy bodies (DLB) Neurodegeneration (α -synucleinopathy) cortical myoclonus • Corticobasal syndrome Neurodegeneration (usually tauopathy) Stimulus-sensitive cortical myoclonus, usually focal affecting one arm, or less frequently one leg, and mostly associated with apraxia or rigidity • Fronto-temporal lobar degeneration due to C9ORF72 mutations Genetic: C9ORF72 (AD) Corticobasal syndrome with dementia, anterior horn cell involvement, parkinsonism, and myoclonus Huntington's disease HTT (AD) Myoclonus can be predominant feature particularly in younger patients with higher triplet repeat numbers; it is cortical, thus stimulus-sensitive and action induced; see text Table 24.7.3.5 Continued (continued)

24.7.3 Movement disorders other than Parkinson's disease 5967 Phenomenology Disorder Aetiology Notes Alzheimer's disease Sporadic or genetic Myoclonus is usually multifocal, but can be generalized, either as single large jerks, or repetitive small ones (at rest, during action, or stimulus-sensitive). It is present in c.50% of patients in middle and late stages of the disease; it may be present early on in those with younger age of onset, rapid progression, and in genetic forms Prion disease Sporadic or genetic Myoclonus is diffuse, generalized, relatively rhythmic, often stimulus-sensitive, and can persist during sleep Myoclonus with encephalopathy Metabolic disturbance Liver failure, renal failure, dialysis related (acute or chronic) disturbance of electrolytes (hyponatraemia, hypocalcaemia) or glucose metabolism (hypo-/nonketotic hyperglycaemia), hypomagnesaemia Often associated with asterixis (negative myoclonus, 'liver flap') and multifocal or generalized myoclonus (spontaneous, stimulus-sensitive). In relation with renal dialysis, there can be both the acute dialysis syndrome, which typically occurs during rapid dialysis and is attributed to cerebral oedema, or the chronic dialysis dementia related to aluminium toxicity Drug-related levodopa, lithium, tricyclic antidepressants, morphine, antibiotics, SSRIs, MAOIs, antipsychotic and anaesthetic agents Toxic bismuth, methyl bromide, tetraethyl lead, mercury, gasoline sniffing, lead benzene, others Acute or subacute onset of clouding of consciousness, epilepsy, and multifocal or generalized myoclonus, which is usually of cortical origin and may occur spontaneously, be stimulus sensitive and action induced encephalitis Infectious (subacute sclerosing panencephalitis, Whipple's disease, Coxsackie, enterovirus, herpes simplex virus, HIV, others), autoimmune/paraneoplastic (including steroid responsive encephalopathy with thyroid antibodies (SREAT), formerly known as Hashimoto's encephalopathy; encephalitis lethargica) Subacute sclerosing panencephalitis (SSPE) is a chronic measles virus encephalitis, which is usually fatal and features characteristic 'hung up jerks' Biotin responsive encephalopathy Genetic: SLC19A3 mutation (AR), gene encodes a thiamine transporter Reported mainly in consanguineous families from the Middle East; Recurrent subacute encephalopathy, often triggered by febrile illness or trauma, with onset in childhood; rarely presentation as chronic disorder or with onset in adulthood; typically widespread involvement with epilepsy, ataxia, dystonia, rigidity, ophthalmoplegia, pyramidal signs. Characteristic MRI finding with T2 hyperintensities and swelling of basal ganglia in

acute stages, and atrophy and necrosis on follow up. Fatal if untreated, but responds to administration of thiamine and biotin Lance-Adams syndrome (postanoxic myoclonus) Hypoxic brain damage Nonprogressive, generalized myoclonus developing days to weeks after hypoxic brain injury; negative myoclonus of legs characteristic (bouncy legs), ataxia, and cognitive involvement present to variable extent (see Video 24.7.3.3) Myoclonus with stiffness Stiff person syndrome and variants, including progressive encephalomyelitis with rigidity and myoclonus (PERM) Autoimmune (+/- paraneoplastic), various antibodies (against GAD, GlyR, amphiphysin, GABA_AR, gephyrin, Ri, DPPX) Spectrum of disorders characterized by stiffness and spasms; see text Acquired hyperekplexia Various aetiologies (brainstem encephalitis; strychnine intoxication; tetanus) Exaggerated startle response to acoustic or tactile stimuli with onset mainly in adulthood; other neurological signs possible Myoclonus with other focal neurological signs Various aetiologies (structural lesions, encephalitis) Myoclonus mimic Functional myoclonus Psychogenic/functional Typical presentation as propriospinal myoclonus; jerks are often distractible, variable, and/or associated with other psychogenic/functional features, like incongruency; 'Bereitschaftspotential' on back-averaging Table 24.7.3.5 Continued

section 24 Neurological disorders 5968 spasms and stiffness, which can give rise to life-threatening neonatal apnoea episodes or induce 'falls en bloque'. Hyperekplexia is a very distinct, but also very rare (incidence unknown) syndrome with genetic and acquired forms. Hereditary hyperekplexia can be caused by several mutations affecting genes mainly involved in glycinergic inhibitory neurotransmission (see Table 24.7.3.5), the classic form being due to mutations in the α -1 subunit of the glycine receptor gene. In hereditary hyperekplexia, symptoms are usually present from birth ('stiff baby syndrome') and may decrease over time with adult patients having only mild, residual signs. The acquired forms are due typically to an autoimmune process targeting glycinergic or gabaergic neurotransmission related to glycine receptor, glu- tamic acid decarboxylase or amphiphysin antibodies (overlap with -> stiff person syndrome). However, brainstem encephalitis of any aetiology, just brainstem lesions, tetanus, and strychnine in- toxication, can give rise to acquired hyperekplexia. Other startle syndromes include startle epilepsy (epileptic seizures triggered by startle, mostly in patients with congenital brain damage) and cul- tural startle syndromes such as the 'jumping Frenchmen of Maine', 'Latah' (Malaysia), and 'Myriachit' (Siberia). Treatment depends on the underlying cause, but benzodiazepines such as clonazepam can be effective as symptomatic therapy. Myoclonus with epilepsy When myoclonus is part of an epileptic syndrome, the term epi- leptic myoclonus is often used. Several syndromes fall into this category, with a wide spectrum from benign and treatable disorders to devastating and treatment refractory epilepsies with marked en- cephalopathy. Epileptic myoclonus is typically accompanied by gen- eralized epileptiform discharges, but the myoclonus itself may be focal, segmental, or generalized. Focal myoclonus can also occur in secondary symptomatic epilepsy due to a lesion. Here we focus on two representative entities where the myoclonus is very much to the fore. For an overview of the whole spectrum, see the Table 24.7.3.5. Juvenile myoclonus epilepsy Juvenile myoclonus epilepsy accounts for 5–10% of all epilepsies. Age at onset is typically in adolescence, but can range from 8 to 25 years. The characteristic semiology consists in myoclonic attacks affecting symmetrically and proximally both arms, and there is a cir- cadian pattern with clustering of attacks in the mornings. Thus, it is often memorized as 'cornflakes epilepsy' as a typical history given by patients is that of spilling the cereals at breakfast. Juvenile myo- clonus epilepsy often occurs in combination with grand mal seiz- ures (90%) upon awakening, or with absences (25%). As

in other idiopathic, generalized epilepsies, seizures can be provoked by sleep deprivation, hyperventilation, or photostimulation. The treatment response overall is good, although lifelong drug therapy is required in most of the cases. However, the manifestation in adolescence renders implementation of the recommended adaptation of lifestyle (regular and sufficient sleep, avoidance of alcohol and recreational drugs) sometimes more difficult.

Familial cortical myoclonus This syndrome is rare and has a confusing number of descriptions, being called ‘benign autosomal-dominant familial myoclonic epilepsy’, ‘familial cortical myoclonic tremor and epilepsy’, or most frequently, ‘familial cortical tremor’ (just to name a few). However, the latter is a misnomer as it only superficially resembles tremor, but is in fact a fine, shivering-like myoclonus most prominent in the hands. It can be associated with generalized seizures. The underlying genetic heterogeneity with several genes (NOL3, ADRA2B, CNTN2) and loci identified might partly explain phenotypical variations stretching from truly benign courses to more progressive and disabling disorders.

Myoclonus with ataxia With his seminal contribution ‘Dyssynergia cerebellaris myoclonica’, James Ramsay Hunt defined a clinical syndrome characterized by progressive myoclonus, ataxia, and epilepsy. Thus, there is a wide variety of underlying aetiologies, with a considerable overlap with the group of progressive myoclonus epilepsies. The myoclonus is of cortical origin and tends to be multifocal or generalized and mainly action induced, but can often also be elicited by stimuli (touch, noise, visual; ‘reflex myoclonus’). The differential diagnosis and further investigations are guided by the associated features, first of all by the presence or absence of cognitive impairment. The so-called ‘famous five’ aetiologies of the progressive myoclonic ataxias comprise Unverricht-Lundborg disease with a relatively benign course and preserved cognition, mitochondrial disorders with a wide phenotypical range, and the storage disorders Lafora body disease, neuronal ceroid lipofuscinosis and sialidoses on the severe end of the spectrum, with prominent dementia and markedly reduced life expectancy (see Table 24.7.3.5).

Unverricht-Lundborg disease or Baltic myoclonus Unverricht-Lundborg disease is the archetypical syndrome of progressive myoclonus ataxia without significant cognitive impairment. Unverricht reported the first family in Estonia, and Lundborg described 10 families in Sweden. Further cases were subsequently noted in Finland, and the term ‘Baltic myoclonus’ was coined since the disease seemed to be common in Scandinavia and related countries. Prevalence rates in Finland were numbered 4–5 in 100 000. The disease is autosomal recessively inherited, and most patients are homozygous for the dodecamer expansion mutation in the cystatin B (CSTB) gene. Age at onset varies between 6 to 15 years (on average 10.6 years), with first symptoms being stimulus-sensitive myoclonic jerks and generalized tonic-clonic seizures, whereas cerebellar signs develop only later. Patients eventually become wheelchair bound, and there may be mild cognitive impairment at later stages of the disease. Pharmacotherapy usually consists of combination therapy with a cocktail of different antiepileptic drugs such as sodium valproate, clonazepam, and levetiracetam. The life expectancy is reduced with an average around 60 years. Although Unverricht-Lundborg disease seems to remain one of the most frequent causes of progressive myoclonic ataxias without prominent cognitive involvement, there are several more recently identified disorders that resemble this phenotype. Autosomal recessive GOSR2 mutations were identified as the cause of ‘North Sea myoclonus’, the name again indicating a clustering of cases in the countries adjacent to the North Sea. Compared to Unverricht-Lundborg disease, this disorder starts earlier in life with ataxia and features scoliosis and potentially other skeletal deformities, and areflexia as distinguishing marks. The list of differential diagnosis keeps expanding by virtue of the advances in the genetics, but also comprises acquired causes like coeliac disease (see Table 24.7.3.5).

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Lafora body disease This rare and fatal disorder is named after the Spanish neuropathologist Lafora who described the characteristic inclusion bodies consisting of polyglucosan. It is autosomal recessively inherited and caused by mutations either in the laforin gene (EPM2A) or in the malin gene (NHLRC1). Either the detection of the gene mutations or the presence of Lafora bodies in biopsied tissue (axilla) are diagnostic. Patients usually present in adolescence with seizures, followed by debilitating myoclonus and dementia. Occipital seizures and visual deterioration are characteristic. Death occurs within 2–10 years after onset.

Neuronal ceroid lipofuscinosis (Batten's disease) Neuronal ceroid lipofuscinosis comprises a group of clinically and genetically heterogeneous disorders characterized by intracellular accumulation of autofluorescent lipopigment. Different subtypes were defined by age of onset, clinical signs, and the ultrastructural pattern of the storage material. The disease runs a relentless course with dementia, epilepsy and progressive visual failure leading to blindness (not in adult onset variant).

Sialidoses Both type 1 and type 2 sialidosis are rare autosomal recessive lysosomal storage diseases. Type 1 is also called 'cherry red spot myoclonus syndrome', because of the red spot in the retina present in nearly all the cases. It begins in the second decade, usually with a progressive loss of vision (deterioration of colour vision, night blindness, retinal degeneration, optic atrophy, corneal clouding). Further features, besides progressive myoclonic ataxia, are generalized tonic-clonic seizures. In contrast, type 2 has an earlier age at onset, a more rapid disease progression and a reduced life expectancy. It also differs from type 1 inasmuch there is dementia, facial dysmorphism, and skeletal dysplasia as additional features.

Opsoclonus-myoclonus This distinct syndrome is also called 'dancing eyes-dancing feet syndrome', a denomination which describes the spontaneous, involuntary, multidirectional, 'chaotic' saccades seen in opsoclonus (see Video 24.7.3.4), and the myoclonus which is often generalized. Ataxia is often a further feature, as are sleep disturbance and behavioural changes. It seems to be immune mediated as it is often paraneoplastic, with neuroblastoma being the most frequent tumour in children, cancer of lung and breast prevailing in adults, but also can be post or parainfectious. In this regard, primary HIV infection is one of the most frequent causes. Sometimes, however, no trigger can be identified. In most cases, no antibody is detected. The therapeutic approach consists of treatment of any underlying malignancy where applicable, and immunotherapy. The outcome is variable, ranging from a monophasic course with excellent recovery to treatment-resistant chronic courses.

Myoclonus with parkinsonism/dementia Myoclonus can be a feature in various neurodegenerative diseases with parkinsonism or dementia as main symptom. Please see Table 24.7.3.5 and Chapter 24.7.2 for more in-depth coverage.

Tremor Tremor is a rhythmic, oscillatory movement, usually due to alternate activation of agonist and antagonist muscles. It can be described according to the body part affected, its frequency and amplitude, and when it occurs, namely at rest vs. posture vs. during movement vs. task or position specific. Kinetic tremor can be further subdivided into action tremor or intention tremor, the latter describing a tremor which increases throughout a performed movement. Tremor may be the sole and defining symptom, or be part of a syndrome with associated neurological signs. Here, we will discuss some specific tremor syndromes in more detail. Table 24.7.3.6 gives an overview of different causes arranged according to their main tremor presentation. Patients often find tremor socially embarrassing and very disabling (Fig. 24.7.3.4). Regardless of the different potentially underlying aetiologies, treatment of tremor is purely symptomatic. Focal tremors (e.g. of head, jaw, voice) often show an excellent response to botulinum toxin injections. Tremor of the limbs often requires medical therapy. Several options (propranolol, clonazepam, primidone, topiramate, and gabapentin) exist, but side effects and potential benefit should be weighed. The first line treatment

for dystonic tremor is trihexyphenidyl, whereas parkinsonian tremors might respond to dopaminergic medication. Orthostatic tremor sometimes responds to clonazepam or levodopa. For severe and disabling tremors, deep brain stimulation is worth considering. Lastly, focused ultrasound may be a noninvasive technique available in the not-so-distant future. Essential tremor

Classically, essential tremor is a symmetrical postural or kinetic tremor of the arms, which gradually worsens over time and which tends to be inherited in an autosomal-dominant manner. Patients often report that small amounts of alcohol tend to decrease the tremor. Additional neurological signs, particularly dystonia, are an exclusion criterion. Isolated voice, tongue, chin, or leg tremor as well as position- or task-specific tremors are not consistent with essential tremor. It is thought to be one of the most frequent neurological disorders with prevalence rates around 300 per 100 000 and a bimodal peak of onset in the second and sixth decade. There are some cases reported with cerebellar or Lewy body pathology, but there is no consistent neuropathological finding. Despite being strongly familial, surprisingly the search for a common causative gene has not been successful so far, although there has been an association with the LINGO1 gene. Thus, it appears that essential tremor is rather a syndrome than a single entity. There are no diagnostic tests for essential tremor, and the diagnosis is based on the clinical findings and exclusion of other causes for postural tremor. In this regard, enhanced physiological tremor comes into the differential diagnosis; this is physiological tremor enhanced by drugs, metabolic, endocrine, or other causes and may be mistaken for essential tremor. Typically, it worsens with anxiety and fatigue, and usually decreases with weight loading as evident on electromyography (EMG). Dystonic tremor

Dystonia itself can be tremulous and may, therefore, manifest as head tremor in patients with cervical dystonia (see Video 24.7.3.5),

section 24 Neurological disorders 5970 a voice tremor (laryngeal dystonia), or hand tremor. Dystonic tremor is often rather jerky and irregular. It can be position- or task-specific (e.g. like primary writing tremor). Recent evidence shows that, rarely, tremor can precede the development of actual dystonia. Often, there is also an autosomal-dominant family history. Again, there are no biomarkers and the diagnosis relies on clinical acumen. It appears that the most common misdiagnoses are essential tremor or benign tremulous Parkinson's disease. However, subtle or not so subtle signs of dystonia (including geste, task and position specificity) and prominent asymmetry mitigate against a diagnosis of essential tremor (Video 24.7.3.6). Where it is difficult to differentiate dystonic tremor from Parkinson's disease on clinical grounds only, a DAT scan is very helpful. Orthostatic tremor

Orthostatic tremor is a rare, but distinct syndrome. Age at onset is typically around 50 years. The patients describe that they feel unstable on standing only and, therefore, have difficulties queuing or during parochial ceremonies. However, they have no difficulty when walking or sitting. The cause is a high-frequency tremor of the legs, which occurs only on standing after a small latency period. Subsequently, with progression of the condition, the tremor becomes more disabling as it occurs straightaway and with higher amplitude. The history suggests the diagnosis itself and, on examination, a high-frequency tremor of both legs can be felt or heard with a stethoscope on the thighs (described as the sound of a helicopter). The tremor is often too fast to be seen, but can be confirmed with EMG, which reveals 13–18 Hz tremor. Sometimes, a postural tremor of the arms can also be observed. In most, orthostatic tremor remains the sole symptom. The few who develop additional features such as parkinsonism or restless legs, are classified as having orthostatic tremor-plus syndrome. The main treatment options are clonazepam and levodopa. Fragile X tremor ataxia syndrome

Fragile X syndrome is one of the most frequent causes for male mental retardation. It is an x-linked condition due to a triplet

re-peat expansion (>200) in the fragile site mental retardation (FMR1) gene. A repeat expansion of 55–200 defines Fragile X permutation carriers, who typically develop a movement disorder characterized by tremor and ataxia called Fragile X tremor ataxia syndrome (FXTAS). FXTAS may sometimes mimic multisystem atrophy, given it can feature a combination of ataxia, parkinsonism, and autonomic dysfunction. However, cognitive impairment which may be present in FXTAS, but not multisystem atrophy, is a red flag. FXTAS can also occur in females, where it is often associated with premature ovarian failure. The brain MRI often shows T2 hyperintensity of the middle cerebellar peduncles (MCP sign). Tic disorders Tics are defined as rapid, brief, stereotyped movements, or vocalizations. In practice, one could think of them as caricatures of normal movements, such as eye blinking, shoulder shrugging, grimacing, sniffing, or grunting. These would be examples of simple motor or vocal tics, whereas complex tics consist of a combined sequence of stereotyped movements or saying words or phrases. Typically, tics wax and wane, and are (temporarily) suppressible, but patients will describe an inner rising tension or anxiety to allow the tics to emerge. This so-called premonitory urge resolves when allowing the tics to happen, and often there is a rebound exacerbation.

Table 24.7.3.6 The main forms of tremor and their most important causes

- Rest tremor • Parkinson's disease ('pill-rolling' tremor) • Atypical parkinsonism (multisystem atrophy, and so on) • Drug-induced parkinsonism • Rubral tremor • Spinocerebellar ataxias • Dystonic tremor • Severe essential tremor • Fragile X-associated tremor/ataxia syndrome (FXTAS) • Neuropathic tremor
- Postural tremor • Enhanced physiological tremor • Metabolic disturbance (e.g. hyperthyroidism, Cushing's syndrome) • Drugs (β -agonists (e.g. salbutamol), anticonvulsants (e.g. sodium valproate), thyroxine, tricyclic antidepressants, theophylline, lithium, immunosuppressive drugs (e.g. cyclosporin)) • Stimulants, drugs of abuse (e.g. coffee, alcohol, nicotine, amphetamine, cocaine, marijuana) • Toxins (e.g. mercury, toluene, solvents) •
- Essential tremor • Neuropathic tremor (e.g. demyelinating neuropathy, particularly with MAG-antibodies or IgM paraproteinaemia) • Dystonic tremor • Parkinson's disease ('re-emergent tremor') • Multiple system atrophy • Spinocerebellar ataxia (esp. SCA 12) • Fragile X-associated tremor/ataxia syndrome (FXTAS) • Orthostatic tremor
- Kinetic tremor • Cerebellar disease (e.g. brainstem or cerebellar outflow pathway lesions, various aetiologies, the most common cause being multiple sclerosis) • Holmes tremor (also called rubral tremor, tripartite tremor (rest < posture < intention) due to damage of cerebello-rubrothalamic and nigro-striatal pathways) • Wilson's disease (often with characteristic 'wing-beating tremor')

24.7.3 Movement disorders other than Parkinson's disease 5971 Primary tic disorders and Tourette syndrome Tics mostly occur as primary disorders without any associated neurological disease. There is a very broad spectrum of tics, spanning from minor tics of self-limiting occurrence during childhood, which occur in up to 15% of school-age children (boys more than girls), and persistent tic disorders, like Tourette syndrome, which can result in significant physical and social disability. Tourette syndrome affects approximately 0.3–0.5% of the adult population, with males being more often affected than females (4:1). Although no gene has been identified, there seems to be a genetic burden since first-degree relatives have a higher risk (10–100-fold), and there are families with an autosomal-dominant inheritance pattern. Our pathophysiological understanding is still limited, but existing data point to a maturation defect of the corticostriatal and corticocortical circuits regulating motor output control, and particularly to altered cholinergic neurotransmission in the striatum. Tourette's syndrome is diagnosed when multiple motor (at least two) tics and vocal utterances (at least one) have occurred (although not necessarily simultaneously) prior to the age of 18 years and persisted for more than one year. Patients with Tourette's might also exhibit

echopraxia (copying movements) or echolalia (repeating words). In contrast, copropraxia (making obscene gestures) or coprolalia (uttering obscenities) are much less frequent. Often however, it is the psychiatric comorbidity (obsessive-compulsive disorder, attention deficit hyperactivity disorder (ADHD), self-harming behaviour, depression) which is much more relevant for the patient's quality of life than the actual tics, and this should be considered in the therapeutic approach. Tics can be treated with dopamine receptor antagonists, A2 receptor antagonists, or benzodiazepines. Botulinum toxin injections can sometimes ease the urge and are considered particularly helpful for vocal tics. Associated psychopathology can be addressed with cognitive behavioural therapy and, if needed, with drug treatment (e.g. SSRI for depression or obsessive-compulsive disorder; methylphenidate for ADHD). Secondary tic disorders More rarely, tics can occur secondarily to neurodegenerative disease (e.g. neuroacanthocytosis, Huntington's disease, Wilson's disease, (a) (b) Fig. 24.7.3.4 Samples of handwriting and spiral drawing from patients with dystonic tremor, illustrating the difficulties patients may face in day to day life on writing or fine motor tasks.

section 24 Neurological disorders 5972 neuronal brain iron accumulation), in developmental disorders (e.g. autism, fragile X syndrome, mental retardation), as part of the spectrum of paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, or due to structural brain damage (e.g. basal ganglia lesions). Lastly, there are certain drugs which are associated with (re-)occurrence of tics (e.g. cocaine, amphetamine, methylphenidate, ecstasy; amantadine, fenfluramine; levodopa; carbamazepine). Restless legs syndrome and other sleep movement disorders Restless legs syndrome Patients with restless legs syndrome complain of the characteristic combination of unpleasant sensations in the legs and an urge to move them as this brings relief. The problem occurs only at rest and usually in the evening. It may be a primary, often familial disorder with an autosomal-dominant inheritance, or secondary, due to a variety of causes including pregnancy, iron deficiency anaemia, peripheral neuropathy, PD, hyperthyroidism, and multiple sclerosis. Several drugs can precipitate restless legs including interferon- α , levothyroxine, neuroleptics, or tricyclic antidepressants. Overall, it is thought to be a relatively common disorder with mild symptoms affecting up to 11% of the population, whereas clinically significant symptoms affect about 3.5%. The pathophysiology is not fully understood. Defective iron metabolism with low iron levels in neuronal cells, particularly in the substantia nigra has been implied, as well as dopaminergic dysfunction. Other studies suggested hyperexcitability or disinhibition of the nociceptive systems. Routine investigations in a patient presenting with restless legs syndrome should include serum ferritin levels, and clinical examination for signs of peripheral neuropathy and parkinsonism. The first-line treatment is dopaminergic medication (L-dopa and dopamine agonists), whereas symptomatic forms can be alleviated by treating the underlying condition (e.g. iron substitution, treatment of uraemia). A caveat of dopaminergic treatment is so-called 'augmentation', referring to a worsening of symptoms (earlier occurrence in the day; increased intensity; involvement of other body parts) during treatment. Periodic limb movement of sleep Periodic limb movement of sleep consists of jerky flexion movements of the hips, knees, and ankles during non-REM sleep. This may be idiopathic, but is often associated with restless legs syndrome, with an overlapping spectrum of symptomatic causes. Treatment with clonazepam is helpful when the disorder causes sleep disruption with consecutive daytime somnolence. REM sleep behaviour disorder It is usually the bed partner who describes the patient shouting, or being punched or kicked out of bed. In REM sleep behaviour disorder, there is no loss of muscle tone during REM sleep, and thus, patients act out their vivid dreams. This may be an idiopathic problem, but often heralds the onset of a parkinsonian disorder, usually with α -synuclein pathology

(Parkinson's disease, dementia with Lewy bodies, multisystem atrophy). In doubt, the diagnosis can be established by polysomnography. Clonazepam or melatonin are useful when sleep quality is poor. Stiff person syndrome and related disorders Moersch and Woltman firstly described stiff person syndrome as a rare and enigmatic disorder of 'progressive fluctuating muscular rigidity and spasm', without other 'firm' neurological signs (Fig. 24.7.3.5). Classical stiff person syndrome features Fig. 24.7.3.5 Paravertebral stiffness leading to lumbar hyperlordosis with skin crease in a patient with classical stiff person syndrome; the hyperlordosis does not even out when bending down.

24.7.3 Movement disorders other than Parkinson's disease 5973 stiffness of paravertebral and proximal muscles, leading to lumbar hyperlordosis and a stiff, wooden gait. Subsequently, a broad clinical spectrum, with stiffness and spasms as the hallmark features, emerged. Often there is also an exaggerated startle response, and falls may occur due to sudden stiffening. We recognize focal forms like stiff limb syndrome as well as progressive encephalomyelitis with rigidity and myoclonus, a variant with a more widespread involvement featuring other neurological signs and a potentially lethal disease course. Apart from the mere motor signs, patients often have a characteristic fear of walking unaided, which leads to them frequently being wrongly labelled as psychogenic. The different variants share a range of associated antibodies, which supports the notion that this is an autoimmune disease, which in some cases is triggered by an underlying neoplasm. Among them, antibodies against glutamic acid decarboxylase, glycine receptor, and amphiphysin are the most frequent and account for up to 90% of the cases. According to current paradigms in neuroimmunology, it is believed that neuronal surface antibodies (see Table 24.7.3.7) are pathogenic whereas the other antibodies, targeting intracellular antigens, are rather a marker of autoimmunity driven by T cells. Apart from antibody testing, the diagnostic work-up includes cerebrospinal fluid analysis and electrophysiological studies (exteroceptive reflexes, continuous motor unit activity). The treatment approach comprises immunotherapy (intravenous immunoglobulins, corticosteroids, plasma exchange, rituximab), removal of tumour where appropriate, and symptomatic treatment with benzodiazepines (mostly clonazepam; high doses may be required and well tolerated) and baclofen. Paroxysmal dyskinesia The paroxysmal dyskinesias are a group of rare, heterogeneous disorders typified by brief self-limiting attacks of involuntary movements, which can be clinically classified according to the triggering factor and the duration of attacks. Between attacks, patients do not have any neurological symptoms. Onset is usually in childhood. Different genetic forms have been identified corresponding to particular clinical phenotypes. Paroxysmal kinesigenic dyskinesia is the most frequent form of paroxysmal dyskinesias with brief (seconds to minutes) attacks of chorea, dystonia or mixed forms precipitated by sudden movement, or even an intention to move or acceleration of ongoing movement (hence kinesigenic). Up to hundred attacks may occur per day. Most cases are due to autosomal-dominant PRRT2 mutations, which also associate with 'Infantile convulsions with paroxysmal choreoathetosis' (ICCA), benign familial infantile epilepsy and migraine. Treatment response to low doses of carbamazepine is usually excellent. Attacks of paroxysmal nonkinesigenic dyskinesias are triggered by alcohol, coffee, or fatigue. They last minutes to hours and are infrequent compared to paroxysmal kinesigenic dyskinesia with just one to three attacks a day and several months of attack free intervals. In familial cases, mutations of the myofibrillogenesis regulator gene MR-1 are the underlying cause. Treatment consists mainly in avoidance of the precipitating factors. Paroxysmal exercise-induced dyskinesia manifests as gradual onset of dystonia in a limb after prolonged exercise of that limb. Heterozygous mutations in the SLC2A1 gene encoding for glu-

glucose transporter 1 (GLUT1) give rise to this phenotype in about half of the cases with paroxysmal exercise-induced dyskinesia. Apart from genetic testing, the diagnosis can be ascertained by measuring the ratio of cerebrospinal fluid to plasma glucose levels, which is below 0.45 in affected subjects. Recognition is important as a ketogenic diet can be used successfully in these cases. There are also secondary forms of paroxysmal movement disorders, for example, due to basal ganglia lesions. The red flags cautioning against a diagnosis of primary paroxysmal movement disorders are a later age at onset, abnormalities on the neurological examination between attacks, and pain during the attacks. The latter is particularly frequent in the tonic spasms seen in demyelinating disorders, and in psychogenic paroxysmal attacks. Of particular interest are two conditions where the paroxysmal attack may herald avoidable damage: limb-shaking transient ischaemic attacks ('limb-shaking TIA') are typically precipitated by rising or exercise, and often accompanied by paresis of the affected limb. They are a manifestation of an internal carotid artery occlusion and indicate a critical haemodynamic state. The so-called faciobrachial dystonic seizures with LGI1-antibodies are very characteristic, brief (<10 s), frequent episodes (up to several hundred per day) of dystonic posturing mainly involving face, arm or leg, or combinations of these, on one side, or alternating. Again, recognition is important as immunotherapy may prevent the development of the full-blown encephalitis.

Table 24.7.3.7 Main antibodies in stiff person syndrome and related disorders

Antibodies against	Glutamic acid decarboxylase (GAD)
Mostly nonparaneoplastic; often associated with other diabetes type 1 and other organ-specific autoimmunity (e.g. thyroid antibodies, vitiligo)	Glycine receptor (GlyR)
a Mostly nonparaneoplastic (malignancies in up to 10%, mostly thymoma, lymphomas, various cancers)	Amphiphysin
Paraneoplastic, often associated with breast cancer	Dipeptidyl-peptidase 6 (DPPX)
a Mostly in PERM variants, prominent gastrointestinal symptoms (diarrhoea or constipation) are a red flag; paraneoplastic and nonparaneoplastic (malignancies in up to 10%, mostly B-cell lymphoma)	Neuronal surface antibodies.

section 24 Neurological disorders 5974 Functional movement disorders A wide variety of drugs can cause different movement disorders, the classical scenarios being that of the tardive dyskinesia and dystonia, or akathisia, due to chronic exposure to dopamine receptor blocking agents. Besides, there are acute and subacute presentations related to initiation of a new treatment, or alteration of plasma levels of established drugs. Drug-induced parkinsonism, spanning from mere lack of spontaneous movements to a mimic of Parkinson's disease, can be seen especially with dopamine receptor blocking drugs. Drug-induced chorea, myoclonus, tics, and tremor are covered in the respective chapters. The key to diagnosis is a thorough history, taking into account that antidopaminergic drugs are also used to treat nausea or dizziness (e.g. metoclopramide, phenothiazine), and that patients may consider some medication not as drugs (e.g. oral contraceptives, herbal medicine). Moreover, intake of stimulants (coffee, alcohol, cigarettes) and illicit drugs should be enquired about. Overall, the treatment approach would be to stop the offending drug, and possibly offer symptomatic treatment. Tardive dystonia, dyskinesia, and akathisia Tardive dystonia characteristically involves axial hyperextension with retrocollis, and when severe can even cause a patch of balding on the back of the head due to the constant friction of the head on chair rests. Tardive dyskinesia typically manifests with a very characteristic picture of orolingual facial stereotyped movements such as chewing, lip smacking, and protrusion or writhing movements of the tongue, but also generalized chorea (see Video 24.7.3.7). The term akathisia comes from the Greek and means 'inability to sit still', describing a compelling need to be

in motion driven by a feeling of inner restlessness. The spectrum spans from discomfort when required not to move, to involuntary lower leg and trunk movements which vary from an occasional foot squirming or leg swinging when seated to constant agitated movements, getting up when seated, pacing around, or tramping on the spot. Akathisia can be severely discomforting. A combination of the different manifestations of tardive disorders is frequently observed. Tardive syndromes are caused mainly by chronic exposure to dopamine receptor blocking drugs and, less frequently, to the short administration or withdrawal of a dopaminergic antagonist or indirect dopaminergic inhibitors, such as SSRIs. Although the pathophysiology is not yet understood, it is assumed that particularly D2 receptor blockade could lead to postsynaptic dopamine receptor hypersensitivity. Other hypotheses invoke secondary maladaptive synaptic plasticity or neurodegeneration. The older anti-psychotics or first generation 'typical' neuroleptics (e.g. haloperidol, flupentixol, sulpiride, chlorpromazine, trifluoperazine, pimozide) are associated with a higher risk of inducing tardive dyskinesia (incidence of 5–7.7% per year) than the atypical antipsychotics or newer generation neuroleptics (e.g. clozapine, quetiapine; incidence 2.9% per year). Tardive movement disorders rarely remit and can cause significant socially stigmatizing physical discomfort. Therefore, it is best to avoid long-term exposure and higher doses of neuroleptics, and to give preference to the atypical neuroleptics. When tardive symptoms occur, the offending drug should be discontinued where possible. The medical treatment options are similar to those otherwise used, namely anticholinergic drugs like trihexyphenidyl for tardive dystonia and tetrabenazine for tardive dyskinesia. Botulinum toxin injections can bring relief in tardive dystonia and there are single reports of good responses to deep brain stimulation of the globus pallidus. Paradoxically, the (re)introduction of dopamine receptor-blocking drugs (e.g. quetiapine, risperidone) can improve tardive dyskinesia or tardive dystonia. Treatment of akathisia is with anticholinergics such as trihexyphenidyl or procyclidine, or benzodiazepines. Acute dystonic reactions Suddenly developing jaw opening dystonia (with or without oculogyric crisis and/or laryngospasm) should raise the suspicion of a drug-induced acute dystonic reaction. These occur shortly (hours to days) after administration of the offending drug. This may be a dopamine receptor blocking agent (neuroleptics, but also antiemetics like metoclopramide), an amine depletor (tetrabenazine), an antidepressant (particularly SSRIs), or a calcium antagonist (flunarizine). Acute dystonic reactions have also been described with benzodiazepines, anticonvulsants, general anaesthetics, and ranitidine, or with cocaine, or ecstasy. The treatment consists of discontinuation of the offending drug, administration of anticholinergics (e.g. benztropine or procyclidine i.v.) and prevention of recurrence by covering with trihexyphenidyl. Neuroleptic malignant syndrome and related disorders Neuroleptic malignant syndrome is a medical emergency, caused either by starting treatment, or by increasing the dose of dopamine receptor blocking drugs, and occurs in approximately 0.5–1% of cases. The combination of rigidity, high fever, hypertension, excessive sweating, and a fluctuating level of consciousness should alert any physician, as this condition can be fatal. There are no diagnostic tests, although creatine kinase and white cell blood count are usually raised. Treatment is in an ICU setting and consists of supportive care, administration of dantrolene as a muscle relaxant, or dopamine agonists, and discontinuation of the dopamine receptor blocker. In patients with Parkinson's disease, sudden discontinuation of dopaminergic drugs can result in a similar clinical picture (parkinsonism-hyperpyrexia syndrome, akinetic crisis). The management is similar, plus reintroduction of the dopaminergic medication. Related disorders are the dyskinesia-hyperpyrexia syndrome, and serotonin syndrome. Dopamine agonist withdrawal syndrome Dopamine agonist withdrawal syndrome is a recently recognized entity, which occurs, however, in as many as 15–19% of patients who discontinue their medication with

dopamine agonists because of side effects, such as impulse control disorder. The symptoms are depression, anxiety, fatigue, insomnia, and autonomic symptoms (postural dizziness, sweating). Most of the patients recover within six months, but some patients are unable to remain off dopamine agonists. Replacement with L-dopa is not helpful, and the fact that there seems to be an association between the risk of developing impulse control disorders and dopamine agonist withdrawal syndrome underlines the challenge to manage these cases.

24.7.3 Movement disorders other than Parkinson's disease 5975 **Functional movement disorders**

Many different terms have been used over the centuries to describe nonorganic symptoms, and currently, the controversy to call them psychogenic or functional continues, fuelled by the increasing recognition of this entity. Overall, it is thought that functional movement disorders account for 2% of all patients, but up to 20% in tertiary referral centres. They occur either in isolation (possibly with other psychogenic symptoms) or on top of an organic disease, as a 'functional overlay'. The difficulty with functional disorders has been that there is often a reservation to make and break the diagnosis, and insecurity about the management. However, the prognosis is better the earlier the diagnosis is made and conveyed. Thus, subjecting the patient to every possible diagnostic test in order to rule out the most remote differential diagnosis is detrimental as it delays, and reinforces the patient's notion that there may be some underlying organic condition. We should keep in mind that an erroneous diagnosis of organic disease is often just as harmful as the misdiagnosis of a functional disorder in an organic disorder. The diagnosis of functional disorders rests upon the recognition of incongruity with any organic disease and positive diagnostic findings suggestive of a functional disorder upon clinical examination. Sometimes there is no psychological stressor identifiable, so the diagnosis should not rely on presence or absence of it. Clues from the history include an abrupt onset, often with a physical or psychological precipitant, variability of symptoms with paroxysmal exacerbations and a change in phenomenology over time. Often there are also multiple additional co-occurring neurological and systemic symptoms. The signs to look out for in clinical examination are distractibility (resolution or diminution of symptoms with distraction; see Video 24.7.3.8), variability (change of pattern; see Video 24.7.3.9), suggestibility (exacerbation when the attention is focused on the affected body part, and improvement with placebo manoeuvres). The 'whack-a-mole' sign describes the shift of symptoms to other body parts, if the affected body part is restrained; for example, a tremor in one limb may appear in another when the former is kept still by the examiner. The 'huffing and puffing sign' describes the inappropriate effort needed for simple tasks. There is frequently 'give-way' weakness of the limbs and a positive Hoover sign, or a functional pattern of sensory disturbance. The disability is often out of proportion to the objective examination findings. There are certain characteristic phenotypes of functional disorders (Box 24.7.3.2). The differential diagnosis comprises organic disorders that can give rise to unusual or even bizarre-looking symptoms (e.g. the gait in Huntington's disease or stiff person syndrome, or paroxysmal movement disorders). Functional disorders must be distinguished from feigning and malingering.

Miscellaneous movement disorders

Hemifacial spasm This is a common condition leading to involuntary muscle twitching of the muscles innervated by the facial nerve. The twitches usually start around the eye, and later spread to involve other muscles on the same side of the face. These muscle spasms are synchronous and occur spontaneously, but can be induced by touch or cold, or facial movement. It affects approximately 7–14/100 000. The so-called idiopathic forms are often caused by irritation of the facial nerve at the root exit zone by an aberrant blood vessel. Secondary forms are seen with lesions in the region of the facial nerve root exit zone, mostly tumours and demyelination. The diagnostic work-up should, therefore, include a MRI scan. In the primary forms, age of onset is

usually in the fourth or fifth decade. There is a preponderance of females, and those with vascular risk factors such as hypertension, diabetes, and hypercholesterinaemia which makes them prone to having tortuous intracranial blood vessels. There are higher incidence rates among Asians. The treatment of choice is botulinum toxin injections. Drug treatment is usually not very effective, and the surgical approach (microvascular decompression) bears significant risks.

Myokymia Myokymia is an involuntary, spontaneous, localized quivering of a few muscles, or bundles within a muscle, but which are insufficient to move a joint. Myokymia has a characteristic EMG pattern of doublets and multiplets. It persists during sleep. Myokymia can be focal, multifocal, or generalized. Immune-mediated forms are seen in Isaac's syndrome (peripheral nerve hyperexcitability with myokymia and neuromyotonia) and Morvan's fibrillary chorea (myokymia plus encephalitis with dysautonomia and insomnia), both due to antibodies targeting the voltage gated potassium channel complex, in particular Caspr2-antibodies. In addition, the venom of the rattlesnake, which also blocks voltage gated potassium channels, can cause myokymia. Genetic forms are caused by KCNA1 mutations affecting potassium channels, as seen in episodic ataxia type 1. Superior oblique myokymia manifests as repeated, brief episodes of rotation and (minimal) downgaze of the affected eye, superficially resembling monocular nystagmus and leading to diplopia. The term, however, is probably a misnomer, as there is no indication of a channelopathy as in the other forms of myokymia, but emerging evidence of neurovascular compression at the root exit zone of the trochlear nerve, a commonality shared with hemifacial spasm.

Box 24.7.3.2 Some well-recognized patterns of psychogenic (functional) movement disorders

- **Functional dystonia** The classical case is that of a young woman, who after a minor trauma acutely develops a painful fixed posturing and in-turning of the foot with trophic and sudomotor changes. There might be a spread of symptoms to other limbs.
- **Functional tremor** Functional tremor is one of the most frequent psychogenic movement disorders. It is distractible (see Video 24.7.3.8) and ceases with ballistic movements of the other limb. Entrainment describes the adaptation of tremor frequency when the patient is asked to perform a rhythmic task at a certain pace dictated by the examiner.
- **Propriospinal myoclonus** It has been recently recognized that propriospinal myoclonus, in most cases, is functional. This notion is, inter alia, based on the occurrence of a Bereitschaftspotential (premovement potential, present in the electro gastrogram (EGG) prior to voluntary movements).
- **Functional gait disturbance** There are various patterns of functional gait disturbance. Patients may walk excessively slow and cautious as if 'walking on ice', or feel they have balance difficulties and veer from side to side, waving their arms, with a narrow base ('tightrope walker gait'), which in fact requires excellent balance.

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