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ESSENTIALS Many disorders of the nervous system, especially the degenerative conditions, have a genetic basis, which is usually due to a mutated gene resulting in decreased production of a critical structural or regu- latory protein. When evaluating a patient with a possible neurodegenerative condition, the following are critical; (1) asking the question, is this a sporadic or inherited condition? (2) taking a detailed family history; (3) establishing an accurate age of onset and history of progression; (4) concentration on the first clinical manifestations of disease, which may give critical clues to diagnosis; (5) conducting a careful general examination, looking for signs outside the nervous system; (6) logical investigation, remembering the key point that, while a clinical diag- nosis of a genetic disorder can be confirmed by the identification of a potentially pathogenic gene mutation in a patient with signs and symptoms consistent with that disorder for whom alternative or coexisting disorders have been excluded, much less diagnostic cer- tainty is provided when genetic testing identifies a gene variant of un- known clinical significance, or when a potentially pathogenic gene variation is discovered in a patient whose clinical syndrome does not conform to the genetic condition. This chapter reviews and provides a guideline for inherited neurodegenerative disease. It is organized in a manner that a good neurological examination would be organized (i.e. systemic dis- orders followed by neurological disorders), discussed in a top-down manner (i.e. from cortex to muscle). Discussion of individual dis- orders starts with the molecular genetics, followed by molecular pathology, histology, clinical features, investigational findings, and management. The disorders are grouped in 12 sections:

1. Neurocutaneous syndromes (phakomatoses)—disorders that pre- sent with skin and brain as their primary organs of affection.
2. Defects in DNA repair—for example, xeroderma pigmentosum, ataxia-telangiectasia, and Cockayne's syndrome, which present with a variety of abnormalities, including in many conditions a propensity to various cancers and skin abnormalities.
3. Metabolic disorders with neurological system as the primary organ of affection, including (1) Leucodystrophies—these are dis- orders which have a genetic basis, a progressive clinical course,

primary involvement of white matter, and a demonstrable bio- chemical or molecular defect. The primary leukodystrophies can be classified into three subgroups: (a) classic dysmyelinative disorders (e.g. X-linked adrenoleukodystrophy, metachrom- atic leukodystrophy); (b) hypomyelinative with delayed or decreased myelin production (e.g. Pelizaeus–Merzbacher dis- ease); and (c) vacuolating myelinopathies (e.g. Canavan's dis- ease). (2) Metabolic disorders (e.g. various mitochondrial and lysosomal storage diseases, amino and organic acidemias, some glycogen storage diseases). 4. Dementing disorders—the genetic basis of common and gen- erally sporadic disorders is discussed, including Alzheimer dis- ease, frontotemporal dementia, Lewy body dementia, and prion diseases. 5. Inherited epilepsy syndromes—these are often caused by defects in genes regulating voltage- or ligand-gated ion channels, but epi- lepsy is also a feature of several lysosomal storage diseases and many other inborn metabolic disorders. 6. Headache disorders—with focus on inherited small vessel disease presenting as migraine, including cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL). 7. Movement disorders—basal ganglia pathology is a principal feature of these conditions, which include Wilson disease, Huntington disease, Parkinson's disease, neuroacanthocytosis, neurodegeneration with brain iron accumulation, and heredi- tary dystonias. 8. Hereditary ataxias—these can be grouped as autosomal dominant ataxias, X-linked and autososmal recessive (e.g. Friedreich ataxia) ataxias, rare but treatable ataxias, and epi- sodic ataxias. Pathology involves primarily the cerebellum and/ or spinocerebellar tracts. 9. Hereditary spastic paraplegias—the pyramidal tracts of the spinal cord are a major site of pathology in this group of conditions, which have extremely wide clinical variability in age of onset, se- verity, course, presence and degree of weakness, and occurrence of other neurologic signs. 10. Motor neuron diseases—including spinal muscular atrophy and amyotrophic lateral sclerosis. 24.17 Inherited neurodegenerative diseases Swati Sathe

section 24 Neurological disorders 6198 11. Disorders of the peripheral nerve—these include autosomal dom- inant demyelinating genetic neuropathies, hereditary sensory, and motor neuropathies, hereditary motor neuropathies. 12. Muscle disorders—these include dystrophinopathies (Duchenne and Becker muscular dystrophy), myotonic dystrophies, limb- girdle muscular dystrophies, distal myopathies, hereditary in- clusion body myopathies, congenital muscular dystrophies, and congenital myopathies. Introduction It is increasingly recognized that numerous disorders of the ner- vous system, especially the degenerative conditions, have a genetic basis. Even so, these disorders may be difficult to recognize as such because of dearth of specific signs, slow progression of symptoms, and lack of definite family history. Inherited neurodegenerative dis- orders present an enormous challenge because of the complexity of the nervous system, the broad clinical and genetic heterogeneity characteristic of these diseases, and the progressive and generally ir- reversible nature of their neuropathology. A mutated gene is

gener- ally at fault, often resulting in decreased production of a structural or regulatory protein important for the development or normal func- tioning of a special part of the nervous system. Neurogenetics combines studies in the fields of Neurosciences and Genetics to understand the role of genes in the development, maintenance, and preservation of function of the nervous system. Unprecedented expansion of knowledge and techniques in the field of molecular genetics has led to great advances in our understanding of the basis of inherited neurological disease. This translates in to the clinical field as availability of a range of molecular, cytogenetic, and biochemical tests, which brings with it the need for a systematic approach to narrow diagnostic possibilities to facilitate judicious use of these tests. This chapter aims to equip the general physician to be able to recognize signs and symptoms of an inherited neurologic disease and initiate work-up. Clinical approach Several factors should be considered in evaluation of a patient pre- senting with a possible neurodegenerative disease. Is the patient's condition sporadic or inherited? Several seemingly sporadic disorders are now known to be late- onset forms of inherited disorders. Very often, especially in cases of lysosomal disorders or enzyme deficiencies, where residual en- zyme activity dictates the phenotype of the disease, late-onset forms with higher residual activity may manifest in a completely different manner. For example, late-onset Tay–Sachs disease presents as a motor neuron and cerebellar disease and thus lacks classic features of infantile Tay–Sachs, namely cognitive decline, seizures, or cherry red spot. Similarly, a divergent mutation, unlike the one known to cause the classic manifestation of a disorder, may modify the pheno- type significantly (e.g. shorter expansion of the trinucleotide repeat presents as adult-onset tremor-ataxia syndrome in case of Fragile X syndrome, quite unlike the mental retardation phenotype seen in young boys with longer repeats). Similarly, late-onset forms an autosomal recessive of disease are very likely to be interpreted as sporadic (e.g. in case of very late-onset Friedreich ataxia, where a presentation as such after the age 40 would otherwise be considered unlikely). Consistent loss of neurological function, involvement of more than one neurological pathways and lack of an obvious ac- quired aetiology should be prompt clinicians to consider the possi- bility of an inherited neurodegenerative disease. Family history A detailed three-generation family history should be obtained with emphasis on any related neurological symptoms, keeping in mind that genetic disorders have variable expression and penetrance. This leads to intrafamilial variability in clinical presentation. In CADASIL, for example, families are described where younger indi- viduals were severely disabled while their senior relatives were much less impaired. Family history may be lacking in autosomal recessive disease or in situations where the index case is adopted. Knowledge of consanguinity is helpful with respect to recessive conditions, and a maternal inheritance pattern, which is especially common in neurological diseases, is consistent with mitochondrial gene dis- order. The clinician interested in neurogenetics should also be- come familiar with other disease-causing genetic mechanisms such as the effects of genetic imprinting (parent-of-origin effect), uniparental disomy, chromosomal disorders, and the effects of spontaneously occurring major rearrangements within and be- tween chromosomes. Modifier genes may also have a profound effect on penetrance (i.e. whether a disease-causing gene is ex- pressed or remains silent). Age of onset and progression Elucidation of the molecular defects in classic forms of neurogenetic disorders has permitted an expansion of the phenotypic spectrum to include both earlier onset of more severe variants as well as later, adult-onset forms of disease. Thus, a practitioner experienced in geriatrics cannot ignore the possibility of a typical childhood-onset disorder first appearing in late adult life, nor can the paediatrician discount the likelihood of a classic adult-onset condition presenting in childhood. The age at which a patient reports that their symp- toms began may not be true age of onset (e.g. patients may report that they became unable

to walk in their twenties in some congenital muscular dystrophies or myopathies, but there is often history of hypotonia, delayed motor milestones, congenital dislocation of hip, or pulmonary infections in infancy). Additionally, in their teens and young adulthood they may have had difficulty keeping up with their peers in sports. This indicates a ‘congenital’ onset rather than ‘late’ onset form of the disease. How did the disease begin? The earliest clinical signs in most inherited diseases of the nervous system refer to one neuroanatomical region or pathology specific to that disease. It may be the cortex as in dementias, the underlying white matter as in many leucodystrophies, the pyramidal tract as in the hereditary spastic paraplegias, the extrapyramidal system affected in various movement disorders, or cerebellar–spinal pathways typical of the spinocerebellar degenerations. It there- fore behoves the clinician to take note of the earliest signs and

24.17 Inherited neurodegenerative diseases 6199 symptoms, and to extract from the examination an indication of the principal anatomical system(s) involved. Delineating and enumerating at the end of the evaluation each subsystem of the nervous system is a good technique (i.e. observe for signs of cor- tical, subcortical, basal ganglia, brain stem, cerebellar, spinal cord, peripheral nerves, neuromuscular junction, or muscle involve- ment), and then consider a disorder or a syndrome that encom- passes those specific pathways. General examination and investigation The presence of extraneural clues such as specific signs involving the eyes, skin, connective tissues, or visceral organs may point towards certain inborn errors of metabolism. Important find- ings that are of particular significance include corneal clouding or cataracts, abnormalities in skin pigmentation, musculoskeletal abnormalities, dysmorphic features, or enlargement of the liver and/or spleen. Important diagnostic clues come from investigations that indicate disorders of pathways involving amino acids, organic acids, lipids, carbohydrates, purines, and pyrimidines, heavy metals, porphy- rins, and vitamins. Based on clinical picture and biochemical tests of urine and blood, it is possible to localize the abnormality to par- ticular subcellular elements such as the mitochondria, lysosome, or peroxisome. Although ultimately DNA analysis will lead to a specific diag- nosis, there are many tools to assist the clinician in obtaining the correct clinical diagnosis. These include various neuroimaging tech- niques, neurophysiology studies, microscopic studies of blood cells and tissue biopsies, and biochemical analyses of blood, urine, cere- brospinal fluid, and cultured skin cells. Judicious choices of confirmatory studies need thoughtful con- sideration of the history, clinical findings, and family history, often in consultation with a neurometabolic disease specialist. A cau- tionary remark regarding DNA testing is appropriate. The clinical diagnosis of a genetic disorder can be confirmed by the identifica- tion of a potentially pathogenic gene mutation in a patient with signs and symptoms consistent with that disorder for whom alternative or coexisting disorders have been excluded. Much less diagnostic certainty is provided when genetic testing identifies a gene variant of unknown clinical significance, or when a potentially pathogenic gene variation is discovered in a patient whose clinical syndrome does not conform to the genetic condition. This is extremely im- portant given the increasing availability of testing with large (and expensive) multigene panels. Management Inherited diseases of the nervous system, particularly as seen in adults, present in a slow progressive manner after a prolonged pre- symptomatic or pauci- symptomatic period of several decades. This creates difficulties in therapeutic attempts to reverse a pathological process that is advanced and already associated with significant cell loss, as well as in counselling and preventing further cases within the same family. Hence, where there are therapies, prospects for new- born screening are being considered. In cases of disorders with se- vere morbidity and/or mortality that are as yet untreatable, prenatal diagnosis, often using pre-

implantation testing, is considered. Use of this technology pre-supposes knowledge of a specific genetic marker within a family for the disease in question. Section I: Neurocutaneous syndromes (phacomatoses) The phakomatoses are disorders affecting mainly the skin along with the central and peripheral nervous systems, characterized by multiple hamartomas and other congenital malformations. Four classical neurocutaneous syndromes include neurofibromatosis, tu- berous sclerosis, Sturge–Weber syndrome, and von Hippel disease. Over the years, more than 60 neurocutaneous syndromes have been described. Affected individuals often have an increased genetic sus- ceptibility to develop malignancies as these diseases involve defects in tumour-suppressor genes. Neurofibromatosis 1 Neurofibromatosis 1 (NF1) (MIM 162200), also called von Recklinghausen's disease, is the commonest of the phacomatoses and one of the most common autosomal dominant disorder, with an in- cidence of 1 in 4000 live births and prevalence of 1 in 5000 without any predilection for ethnicity or gender. It is often inherited from a more mildly affected parent; random somatic mutation of the one re- maining functional NF1 gene is believed to be required for tumour formation. The NF1 gene that maps to chromosome 17q11.2, codes for neurofibromin. Diverse functions of protein neurofibromin are impli- cated in the breadth of clinical and imaging manifestations seen in pa- tients with NF-1. The functions of the NF1 gene include: (1) Tumour suppression via negative regulation of the p21 RAS proto-oncogene. (2) Regulation of neural stem cell proliferation, survival and astroglial differentiation, and neuroglial progenitor function. (3) Maintenance of the vascular wall. (4) Normal myelination by Schwann cells: the gene for oligodendrocyte myelin glycoprotein, a major myelin protein, is em- bedded within intron 27b of the NF1 gene. (5) Bone formation and re- modelling. Thus, alteration in the function of neurofibromin leads to abnormalities of brain formation (especially myelination), tumours, vascular lesions and osseous abnormalities/skeletal dysplasias. NF1 may be suspected in early childhood but will not develop into the full-blown condition for several years. The first feature to appear are café-au-lait macules, which may be present as early as at birth or appear during the first few months of life. There must be six or more café-au-lait spots to meet diagnostic criteria. Freckling in areas not exposed to sun such as the axilla occurs next, usually by school age, followed by development of Lisch's nodules, which are melanotic hamartomas of the iris that can be seen as whitish, yellow, or brown spots on visual inspection in patients with light-coloured irises, but often require slit-lamp examination. Dermal neurofibromas ranging from a few millimetres to a centimetre or more appear at puberty, which are made of Schwann cells, fibroblasts, and mast cells. They are flesh coloured; when pressed, they invaginate through the skin ('button-holing'). Patients may have only a few or may have thou- sands of these 'mollusca fibrosa'. These tumours may be cutaneous or subcutaneous, or extend into multiple nerves forming plexi- form neurofibromas (Fig. 24.17.1) producing diffuse enlargement of major nerve trunks. About 40% of patients develop plexiform neurofibromas, which have a 5–10% risk of malignant transform- ation with poor overall survival rate. A small percentage of patients develop optic pathway gliomas, which do not appear to cause any ophthalmological symptoms. Scoliosis occurs in 21% of patients and may be dystrophic or nondystrophic; the latter is characteristic of

 NF1, is rapidly progressive, and has a worse prognosis (Fig. 24.17.2). Phaeochromocytoma, renal artery stenosis, and precocious pu- berty are also encountered. Learning disabilities, attention deficit disorder, intellectual impairment, seizure disorder, and psychi- atric manifestations may appear in a small percentage of patients. Pilocytic astrocytomas also develop most commonly in the optic nerve, chiasma, and tract. Focal neurologic signs may be caused by dumbbell shaped neurofibromas arising from nerve roots with extraspinal

and intraspinal components. Patients may therefore present with signs and symptoms of spinal cord compression or cauda equina syndrome. Diagnostic criteria for NF1 are enumer- ated in Box 24.17.1. Segmental NF is described in individuals with the mosaic form of NF1 with features usually limited to one or more regions of the body. A somatic mutation that occurs late in embryonic develop- ment can result in disease localized to a segment. Patients are still susceptible to NF complications or transmission to offspring. Brain magnetic resonance imaging (MRI) T2-weighted images re- veal high-intensity, nonenhancing lesions, most often found in the brainstem, thalamus, cerebellum, and basal ganglia but not in sub cortical white matter. These tend to disappear by late adolescence or early adulthood. Optic pathway gliomas involving the optic nerves, chiasm and frequently the optic tracts are seen in about 20% of NF1 patients almost always before the age of six years (Fig. 24.17.3). Common vascular abnormalities seen on imaging include stenoses, occlusions, ectasia, moyamoya disease, and fusiform aneurysm for- mation. Skeletal changes associated with mesodermal dysplasia in- clude posterior vertebral body scalloping; thinning of the pedicles, transverse processes, and lamina; foraminal enlargement; sphenoid wing dysplasia and cortical thinning; periosteal proliferation; scler- osis; and bowing of the long bones (Fig. 24.17.2). The goals of evaluation and follow-up are to confirm the diagnosis of NF, provide genetic counselling, detect emergence of treatable complications, and optimize quality of life. Plexiform neurofibromas causing pressure symptoms may necessitate excision and others may merit removal for cosmetic reasons; they often recur. Rapid expan- sion of a tumour, the development of pain, and loss of neural func- tion suggest malignant change, and this occurs most often during adolescence or in young adults. Early treatment with wide surgical resection, with or without adjuvant chemotherapy or radiotherapy is indicated. Development of hypertension will require investigation for phaeochromocytoma, and spinal deformity may need ortho- paedic attention. Follow-up annually in a multidisciplinary neuro- fibromatosis clinic is advisable. Neurofibromatosis 2 Neurofibromatosis 2 (NF2) (MIM 101000) is also autosomal dom- inant but is much less common than NF1 with a frequency of 1 in 40 000 live births and prevalence of 1 in 200 000. The NF2 gene is located on the long arm of chromosome 22 and encodes merlin or schwannomin, a protein expressed in neurons, the lens of the eye, blood vessels, leptomeningeal cells, astrocytes, gonadal tissue, and Schwann cells. As in the case of neurofibromin, merlin mediates growth suppression, and the development of NF2 requires a second hit to the remaining normal NF2 gene. The loss of NF2 expression is also seen in 30–70% of sporadic meningiomas and almost all sporadic schwannomas. NF2 has minimal cutaneous and no skel- etal abnormalities. The principal manifestation is bilateral vestibular schwannomas associated with multiple meningiomas, cranial nerve tumours, optic gliomas, and spinal tumours (Fig. 24.17.4). Diagnostic criteria for NF2 are listed in Box 24.17.1. Patients who meet some of the criteria of NF2 but not enough to confirm the diag- nosis should receive regular follow-up. They may eventually develop other manifestations, thus confirming the diagnosis. Adults present with unilateral hearing loss often associated with tinnitus. The Wishart form, usually associated with a truncating mu- tation, presents earlier with faster progression of lesions leading to deafness, cataracts, and focal neurological deficits. The milder or Gardner form presents later in life with relatively stable tumours over years. Recommended diagnostic testing includes brain MRI with at- tention to internal auditory canal and spinal MRI to assess for tu- mours. In cases of bilateral hearing loss, a cochlear implant may be beneficial. Surgical treatment remains a cornerstone of manage- ment for symptomatic and progressive vestibular schwannomas, meningiomas, and spinal tumours. Vascular endothelial growth factor inhibitors have shown promising results for in delaying sur- gery for vestibular schwannomas, and other targeted molecular therapies are investigational options. Tuberous

Sclerosis Complex (Bourneville's disease) Tuberous sclerosis complex (TSC) (MIM 191100) is a disorder of cellular differentiation and proliferation that affects the brain, skin, kidneys, heart, and other organs. The disorder is domin- antly inherited with a birth incidence of 1:6000–9000, but may be transmitted by individuals who are asymptomatic or show only minimal clinical evidence of the disease. Isolated cases are fre- quent, making up as many as 80 or 90% of index cases; two thirds may represent new mutations. Genetic heterogeneity has now been established, with separate loci on chromosomes 9q34 (TSC1) and 16p13.3 (TSC2). The TSC1 gene product hamartin and the
Fig. 24.17.1 Internal plexiform neurofibroma. Coronal MRI shows an extensive neurofibroma (asterisk) in an eight-year-old boy with neurofibromatosis type 1. Reprinted from The Lancet 13(8), Hirbe AC and Gutmann DH, Neurofibromatosis type 1: a multidisciplinary approach to care, pages 834–43, Copyright © 2014, with permission from Elsevier.

24.17 Inherited neurodegenerative diseases 6201 TSC2-derived protein tuberin form a functional heterodimer that results in downstream inhibition of mTOR (mammalian target of rapamycin), a serine-threonine kinase implicated in the activa- tion of translation regulators involved in the expression of many proteins in cell proliferation and growth (Fig. 24.17.5). Tuberin also binds p27, which has been implicated in regulating cell cycle progression. Glutamatergic and GABAergic neurotransmission abnormalities have been demonstrated in the tubers, which may underlie epilepsy and intellectual disability seen in tuberous scler- osis (TS). Mutations are identified in 85% of patients with TS, 85% of those are in TSC2. Those with TSC1 mutation have a less severe disease phenotype. Many clinical features of TSC result from hamartomas, but true neoplasms also occur, particularly in the kidney and brain. Impaired cellular interaction causes disruption of neuronal migration along radial glial fibres and abnormal proliferation of glial elements; ab- normal neuronal migration plays a major role in neurological dys- function. Neuropathological lesions include subependymal nodules (SENs), cortical and subcortical hamartomas (tubers), areas of focal cortical hypoplasia, and heterotopic grey matter. SENs com- monly arise from germinal matrix progenitors and can grow over time, but eventually calcify by adolescence. These may enlarge and transform into subependymal giant cell astrocytomas (SEGAs) (Fig. 24.17.6). Tubers develop between 14 to 16 weeks of gestation Fig. 24.17.2 Skeletal abnormalities in individuals with neurofibromatosis type 1. Plain film radiographs showing: (a) dystrophic scoliosis (asterisk) in an 11-year-old girl; (b) tibial bowing (asterisk) in a 10-month-old baby girl; (c) tibial pseudarthrosis (asterisk) in a
nine-month-old baby girl; and (d) tibial pseudarthrosis after insertion of an internal rod (asterisk) in a nine-year-old boy. Reprinted from The Lancet 13(8), Hirbe AC and Gutmann DH, Neurofibromatosis type 1: a multidisciplinary approach to care, pages 834–43, Copyright © 2014, with permission from Elsevier.

section 24 Neurological disorders 6202 and frequently extend as linear or wedge-shaped lesions from ven- tricle wall to the cortical surface. Thus, the tuber load is established before birth. Focal cortical malformations (Fig. 24.17.7) involve one gyrus at a time, but more diffuse involvement may lead to hemimegalencephaly. Histologically, these areas demonstrate disor- ganized cortical lamination, abnormal myelination, and indistinct grey/white differentiation. Classic clinical features of tuberous sclerosis are intellectual impairment, infantile spasms, epilepsy, occurrence of retinal hamartomas, and characteristic skin lesions (Table 24.17.2). The earliest cutaneous lesions are irregular foliate areas of depigmentation, hypomelanotic macules or ash leaf spots, over the trunk. These patches are readily identified when viewed under ultraviolet (UV) illumination using Woods'

lamp. Presence of three or more patches is required for diagnosis as these may be seen in normal individ- uals. Facial angiofibromas (‘adenoma sebaceum’) (Fig. 24.17.8) are another type of skin lesions that develop over the cheeks in a ‘butterfly’ distribution and on the forehead with multiple small warty elevations. Finally, a ‘shagreen patch’ may be present over the lower back. This consists of an area of elevated roughened skin with a yellowish tinge, which has been likened to sharkskin. An ungual or periungual fibroma is present after puberty and in adult life. The cerebral malformations give rise to intellectual impair- ment, which is evident in early life and may be static or involve a slowly progressive cognitive decline, often complicated by a be- havioural disorder. Common neurological manifestations of TSC are mental retardation, seizures, and behavioural abnormalities. Milder forms of the disease with little or no neurological impair- ment are common even in parents of affected children. Seizures develop during first year of life and are of various types; recur- rent generalized or focal seizures occur in 80% to 90% of patients; one-third of children with TSC develop infantile spasms. Infantile spasms are indicative of more cortical lesions and worse cognitive impairment. In addition to intellectual disability, many children with TSC have serious behavioural disorders such as autistic be- haviour, hyperkinesis, aggressiveness, and frank psychosis. The prevalence of autistic spectrum disorders is 25% to 50% in pa- tients with TSC. SEGAs develop in 6% to 14% of patients with TSC. When enlarged, they cause symptoms of increased intracra- nial pressure due to an obstructive hydrocephalus, which mani- fests as new focal neurological deficits, behaviour change, or worsening seizures. Box 24.17.1 Diagnostic criteria for NF1 and NF2 Diagnostic criteria for NF1: • The patient must have two or more of the following: 1 Six or more café-au-lait macules measuring 1.5 cm or larger in a postpubertal or 0.5 cm or larger in a prepubertal patient 2 Two or more neurofibromas or one or more plexiform neurofibromas 3 Skinfold freckling in the axilla or groin 4 Optic nerve glioma 5 Two or more iris hamartomas (Lisch nodules) 6 A distinctive bony lesion such as dysplasia of the sphenoid bone or thinning of a long-bone cortex (pseudarthrosis) 7 A first-degree relative (i.e. parent, sibling, or offspring) with NF1 diagnosed by the above criteria Diagnostic criteria for NF2: • The patient must have either of the following: — Bilateral VS — A first-degree relative with NF 2 and either unilateral VS at age younger than 30 years; or any 2 of the following: meningioma, schwannoma, glioma, juvenile posterior subcapsular lenticular opacity Fig. 24.17.3 Low-grade glial neoplasms. (a) MRI showing an optic glioma in the left optic nerve (asterisk) of a four-year-old boy with neurofibromatosis type 1. (b) MRI showing a brainstem glioma (asterisk) in a nine-year-old boy with neurofibromatosis type 1. Reprinted from The Lancet 13(8), Hirbe AC and Gutmann DH, Neurofibromatosis type 1: a multidisciplinary approach to care, pages 834–43, Copyright © 2014, with permission from Elsevier.

 Fig. 24.17.4 Bilateral vestibular schwannomas are characteristic of NF2. (a) Small bilateral vestibular schwannomas. (b) Medium-sized vestibular schwannomas that are compressing the brainstem. (c) Giant bilateral vestibular schwannomas that are compressing the brainstem and causing hydrocephalus. Reprinted from Otolaryngologic Clinics of North America 48(3), Slattery WH, Neurofibromatosis Type 2, pages 443–60, Copyright © 2015, with permission from Elsevier. RAPTOR TBC1D7 GTP Rheb ATP, amino acid and lipid production Glucose metabolism Nucleotide synthesis Lysosomal biogenesis Mitochondrial biogenesis Autophagy mLST8 PRAS40 mTOR mTORC1 Rheb GDP Rapamycin and other mTORC1 inhibitors DEPTOR Protein synthesis Tsc protein complex TSC1 TSC2 p p Fig. 24.17.5 TSC protein complex and mTOR signalling. Reprinted from Pediatric Clinics of North America 62(3), DiMario FJ, Sahin M and Ebrahimi-Fakhari D, Tuberous Sclerosis Complex, pages 633–48, Copyright © 2015, with

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section 24 Neurological disorders 6204 Computed tomography (CT) best demonstrates the calcified SENs of TSC. SENs may extend into the ventricles to produce an appearance that was considered to resemble ‘candle guttering’. Gliomas sometimes arise in these lesions. Brain MRI shows evidence of abnormal neuronal migration as high-signal linear lesions running perpendicular to the cortex. Retinal tumours, termed phacomas or hamartomas (Fig. 24.17.9), may be present, and cardiac rhabdomyomas occasionally arise as well as hamartomas of the lungs and kidneys. Renal angiomyolipomas presenting by age of 10 years may occur in up to three-fourths of patients with TSC. Most of these lesions are benign with varying amounts of vascular tissue, fat, and smooth muscle; they may be bi- lateral. Polycystic disease of the kidneys may also be associated. Treatment goals in TSC are to control epilepsy and maximize cognitive function and learning. Periodic evaluation to monitor emerging symptoms and signs is needed. Two approved treatments for infantile spasms are oral vigabatrin and injectable adrenocortico- tropic hormone (ACTH) preparation. Broad-spectrum antiepileptic agents are usually necessary for ongoing treatment of epilepsy in patients. Corpus callosotomy is an option in young children with refractory seizures as is resective epilepsy surgery in individuals with seizures localizing to a single tuber. Temporal lobectomy or hemispherectomy may be considered in patients with medically re- fractory epilepsy. Vagal nerve stimulator implant may be beneficial for patients with refractory partial seizures. Although not specific for TSC, behavioural and learning disabilities such as attention deficit hyperactivity disorder and autism spectrum Fig. 24.17.6 Subependymal giant cell astrocytoma. Reprinted from Pediatric Clinics of North America 62(3), DiMario FJ, Sahin M and Ebrahimi-Fakhari D, Tuberous Sclerosis Complex, pages 633–48, Copyright © 2015, with permission from Elsevier. Fig. 24.17.7 Cortical dysplasias (dysplasia, tubers, and migration lines). Reprinted from Pediatric Clinics of North America 62(3), DiMario FJ, Sahin M and Ebrahimi-Fakhari D, Tuberous Sclerosis Complex, pages 633–48, Copyright © 2015, with permission from Elsevier. Fig. 24.17.8 Facial angiofibromas. Reprinted from Pediatric Clinics of North America 62(3), DiMario FJ, Sahin M and Ebrahimi-Fakhari D, Tuberous Sclerosis Complex, pages 633–48, Copyright © 2015, with permission from Elsevier. Fig. 24.17.9 Retinal hamartoma. Reprinted from Pediatric Clinics of North America 62(3), DiMario FJ, Sahin M and Ebrahimi-Fakhari D, Tuberous Sclerosis Complex, pages 633–48, Copyright © 2015, with permission from Elsevier.

24.17 Inherited neurodegenerative diseases 6205 disorders require educational assistance as well as psychotropic and stimulant medications. SEGAs may require surgical removal if they are growing or symptomatic. Newer option of stereotactic radio- therapy (SRT) is available. TSC1 or TSC2 gene products are involved in the inhibition of the mammalian target of rapamycin pathway (mTOR), which regulates cell growth and proliferation. Loss of TSC1 or TSC2 leads to overactivation of mTOR and uncontrolled cellular proliferation. Everolimus is an allosteric mTOR inhibitor approved for use in subependymal giant cell astrocytoma. Renal tumours require resection or arterial embolization therapy if there is bleeding, pain, or malignant transformation. Facial angiofibromas have been successfully treated by laser ablation especially when rapidly growing, bleeding, or crusting; however, they may recur (Box 24.17.2). Von Hippel–Lindau disease The von Hippel–Lindau (VHL) disease (MIM 193300) is an auto- somal dominant disorder caused by heterozygous mutations in the VHL tumour-suppressor gene (3p25.3, which encodes a 232-amino-acid protein (pVHL). pVHL plays a key role in cellular oxygen sensing through ubiquitylation and proteasomal degradation of its targets hypoxia-inducible factor (HIF)–1 and HIF-2. In turn, this

affects the upregulation of vascular endothelial growth factor (VEGF), platelet-derived growth factor-β (PDGF-β), transforming growth factor alpha (TGF-α), and erythropoietin substances. VHL lesions obey the classic Knudson 2-hit hypothesis in which sec- ondary inactivation of the nonmutated pVHL allele leads to loss of pVHL function. This results in failure of polyubiquitination and proteasomal degradation of HIF, which is central for the patho- genesis of the disease. The resulting high levels of HIF create a state of pseudohypoxia leading to transcriptional activation of genes linked to erythropoiesis, angiogenesis, and cell metabolism. This proves conducible to the development of highly vascularized tu- mours typical of VHL and the commonly observed erythrocytosis in affected patients. Most recently, HIF-independent pVHL functions have also been uncovered that may play a role in VHL tumorigenesis. Those include apoptosis regulation, cell senes- cence control, microtubule stabilization and maintenance of the primary cilium, and regulation of extracellular matrix forma- tion and cell–cell adhesion. Some sporadic renal cell carcinomas, hemangioblastomas, and pheochromocytomas also harbour VHL biallelic inactivation, thus corroborating the role of pVHL func- tion loss in development of tumours. The VHL syndrome, thus, is associated with an increased risk of developing various benign and malignant tumours including retinal capillary haemangioblastomas (RCH) or retinal angioma and central nervous system haemangioblastomas (CNS HB), hem- angiomas of the adrenal gland, liver, and lung, paragangliomas, phaeochromocytomas (PHEO), renal cysts and clear cell renal cell carcinomas (ccRCC), endolymphatic sac tumours (ELST) as well as pancreatic cysts, pancreatic neuroendocrine tumours (PNET) and cystadenomas of the epididymis and the broad liga- ment (Table 24.17.1, Fig. 24.17.10, pictures 1–7). Box 24.17.2 Diagnostic criteria for tuberous sclerosis complex Major Features 1 Facial angiofibromas or forehead plaque 2 Nontraumatic ungual or periungual fibroma 3 Hypomelanotic macules (more than three) 4 Shagreen patch (connective tissue nevus) 5 Multiple retinal nodular hamartomas 6 Cortical tuber*

- When cerebral cortical dysplasias and cerebral white-matter migration tracts occur together, they should be counted as one rather than two features of tuberous sclerosis. 1 Subependymal nodule 2 Subependymal giant cell astrocytoma 3 Cardiac rhabdomyoma, single or multiple 4 Lymphangiomyomatosis† † When both lymphangiomyomatosis and renal angiomyolipomas are pre- sent, other features of tuberous sclerosis should be present before a definite diagnosis is assigned. 1 Renal angiomyolipoma† Minor Features 2 Multiple randomly distributed pits in dental enamel 3 Hamartomatous rectal polyps‡ ‡ Histological confirmation is suggested. 4 Bone cysts§ § Radiographical confirmation is sufficient. 5 Cerebral white-matter radial migration lines*, †, ‖ ‖ One panel member felt strongly that three or more radial migration lines should constitute a major sign 6 Gingival fibromas 7 Nonrenal hamartoma‡ 8 Retinal achromic patch 9 Confetti skin lesions 10 Multiple renal cysts‡ — Definite tuberous sclerosis complex: either two major features or one major feature plus two minor features. — Probable tuberous sclerosis complex: one major plus one minor feature. — Possible tuberous sclerosis complex: either one major feature or two or more minor features. Reprinted with permission from Roach, E.S., Gomez, M.R., Northrup, H., 1998. Tuberous sclerosis consensus conference: revised clinical diagnostic criteria. J Child Neurol 13, 624–8, Copyright © 1998, SAGE Publications. Table 24.17.1 Von Hippel–Lindau (VHL)-associated tumours Location Tumour Central nervous system haemangioblastomas (HB) Eyes retinal capillary haemangioblastomas (RCH) Petrosal bone endolymphatic sac tumours (ELST) Pancreas pancreatic cysts, neuendocrine

tumours (PNET) Kidney renal cysts, clear cell renal cell carcinomas (ccRCC) Adrenal glands phaeochromocytomas (PHEO) Epididymis, broad ligament cystadenomas Reprinted from Schmidt S et al. (2014) Management of von Hippel–Lindau Disease:
An Interdisciplinary Review. Oncol Res Treat 37, 761–71.

section 24 Neurological disorders 6206 This tumour predisposition syndrome has an incidence of 1:36 000 newborns and estimated prevalence in Europe is about 1–9/100 000. Age dependent penetrance reaches approximately 95% by age 65 years. De novo mutations occur in about 20% of the cases. In patients with positive family history, clinical diagnosis of VHL disease can be made based on finding a single VHL-associated tumor and in cases that lack a positive family history, presence of at least 2 VHL-associated tumours is required for the diagnosis. Suspected cases should be referred for genetic screening of the VHL gene for mutations. Of note, homozygous mutations result in familial erythrocytosis-2 (ECYT2; 263400). Clinical classification is based on the genotype phenotype correl- ation. Type 1 is generally caused by whole or partial gene deletion or nonsense mutation; pheochromocytoma is not one of its features. In type 2 variant is associated with missense mutations and is charac- terized by pheochromocytomas. Type 2 disease is subdivided type 2A (low risk of renal cell carcinoma), type 2B (high risk of renal cell carcinoma), and type 2C (pheochromocytoma only). Common pancreatic lesions include benign cystic disease including microcystic or serous adenomas, which occur in up to 70% of patients with VHL and are often discovered incidentally during abdominal imaging screening. Pancreatic NETs, though nonfunctioning, can occasionally present with abdominal pain, nausea, or diarrhoea. These lesions may cause compression of the main pancreatic duct, pancrea- titis, and compression, or invasion of adjacent organs. The mean age at diagnosis in patients with VHL disease is lower than in sporadic cases (35 versus 58 years), which is probably related to periodic screening. Pheochromocytomas occur only in type 2 VHL disease and are adrenal or extra adrenal, bilateral, and asymptomatic. Similar to pan- creatic NETs, pheochromocytomas also tend to be diagnosed approxi- mately 20 years earlier in familial than in sporadic cases. Malignant disease is relatively rare. The retinal lesions consist of angiomatous vascular malformations. The cerebellar lesion is a haemangioblastoma, often cystic, which may slowly expand and require surgical treat- ment. Such tumours may be associated with polycythaemia. VHL: screening for affected or at-risk individuals:

1. Careful ophthalmic examinations every 12 months beginning in infancy or early childhood
2. MRI scans of the head (±spine) every 12–36 months beginning in adolescence to detect presence of CNS hemangioblastomas
3. MRI scans of the abdomen every 12 months from age 16 years for renal cell carcinoma Retinal haemangio- blastomas, see picture 3 and 4 Phaeochromocytomas, see picture 5 Pancreatic cysts, pancreatic neuroendocrine tumours (=PNET) Cystadenoma of the epididymis and the broad ligament Renal cysts and clear cell carcinomas (=ccRCC), see picture 7 A–C Endolymphatic sac tumours (=ELST), see picture 6 A and B CNS and spinal Haemangioblastomas, see picture 1, 2 A and B Picture 1 Picture 2 Picture 3 Picture 4 Picture 5 Picture 6 Picture 6 Fig. 24.17.10 Picture 1: T1-weighted image of the cerebellum with bilateral cystic haemangioblastomas (HB). Picture 2: Sagittal magnetic resonance imaging (MRI) of the cervical spine shows four small HB at the fourth ventricle, medulla oblongata, and cervical cord (white arrows in (B)). No tumour-associated cysts or syringomyelia are present. Minimal oedema of one tumour can be seen on T2-weighted images (black arrow in A). (A) T2-weighted, (B) enhanced T1-weighted MRI, sagittal view.

Pictures 3 and 4: Fundus photography (3) and fluorescein angiography (4) of a retinal capillary haemangioblastoma (RCH). Picture 5: A small strong enhancing phaeochromocytoma of the left adrenal gland can be identified after the application of gadolinium (arrow). Enhanced T1-weighted MRI in arterial phase, coronal view. Picture 6: Endolymphatic sac tumour of the left side
(thick arrows) with typical destruction of the posterior wall of the petrosal bone. At the posterior margin of and contralateral to the tumour, parts of the sigmoid sinus are visible after gadolinium application (thin arrows). AT2-weighted, B enhanced T1-weighted MRI, axial view. Picture 7: Clear cell renal cell carcinoma (ccRCC) in two different patients.
A small early and strong enhancing carcinoma can be seen in the upper part of the left kidney (white arrow in (A)), showing similar contrast to the normal kidney during parenchymal phase (white arrow in (B)). Simple kidney cysts can be depicted best during parenchymal phase (open arrows (A) and (B)). (C) shows multifocal ccRCC of the lower part of the left kidney with inhomogeneous contrast enhancement (white arrows in (C)). Note multiple pancreatic cysts in the same image (open arrow in C). (A) and (C) Enhanced T1-weighted MRI, arterial phase, (B) enhanced T1-weighted MRI, parenchymal phase, coronal view. Reprinted from Schmidt S et al. (2014) Management of von Hippel–Lindau Disease: An Interdisciplinary Review. Oncol Res Treat 37, 761–71. Fig. 24.17.10 Continued

24.17 Inherited neurodegenerative diseases 6207 4. Yearly screening for phaeochromocytoma beginning in early childhood: 24-h urine studies to measure catecholamine me- tabolites and measurement of plasma normetanephrine levels; the latter is reported to be the most sensitive test for detecting phaeochromocytoma. Patients with VHL require imaging of the CNS and spinal cord, monitoring of blood pressure and catecholamine metabolites, and an annual eye examination. Surgical removal is required for symp- tomatic tumours. Although, primary treatment of all VHL-related tumours is local, systemic therapy is warranted when there are re- peated local interventions at multiple sites or repeated recurrences in one area or progression of inoperable and previously irradiated tumours. Sunitinib, a multi-target tyrosine kinase inhibitor, is being investigated in a phase II trial in patients with VHL. Multiple other agents are currently under clinical investigation as potential treat- ments for hemangioblastoma. VEGF-targeting agents are a reason- able choice in keeping with the pathophysiology in most tumours. Bevacizumab is a humanized monoclonal antibody that binds to the soluble VEGF and inhibits its interaction with the VEGF re- ceptor. It has been demonstrated to be efficacious in patients with hemangioblastoma and renal cell carcinoma. Oral anti-VEGF agent, PTK787/ZK222584 which targets all known VEGF receptor tyrosine kinases and TKI-538, an anti-angiogenic multikinase inhibitor, are currently under investigation in phase II trials for the treatment of hemangioblastoma in patients with VHL, while histone deacetylase (HDAC) inhibitor vorinostat is also in phase I clinical trial. Given enormous lifelong impact on quality of life, early molecular genetic testing of the children of an affected VHL parent is strongly recommended. A comprehensive paediatric-screening programme to detect tumours should be started as early as possible. VHL dis- ease is a challenging systemic disease that has better outcomes with continuous medical surveillance and treatment is best approached in an interdisciplinary fashion. This chronic unpredictable disease has major implications on various important matters like career and em- ployment, health insurance, and family planning. Psychological stress and insecurity should not be underestimated and properly managed. Sturge–Weber syndrome Sturge–Weber Syndrome (SWS, also known as encephalofacial angiomatosis, MIM 185300) is a sporadic congenital condition caused by a somatic activating

mutation in GNAQ. The classic manifestation is a capillary malformation of the skin, port-wine birthmark, also known as port-wine stain/nevus, in the V1 distribution of the face (forehead and/or eyelid); V2 and V3 distributions may be involved. This may be associated with cerebral venous malformations (leptomeningeal angiomatosis), and ocular capillary venous vascular malformations causing glaucoma. Venous angioma containing dilated and tortuous deep cerebral veins is confined to the piamater. Chronic venous stasis forms the basis of progressive calcification of underlying brain paren- chyma starting with deep cortical layers spreading to the upper layers. Progressive brain atrophy succeeds the calcification. Bilateral port- wine nevus is associated with a higher risk of brain involvement. Epilepsy, owing to the brain calcification and atrophy, is the most frequent neurological feature in 75–80% of patients, followed by intel- lectual impairment, migraine, stroke-like episodes, and focal neuro- logical deficits are frequent. All seizure types may occur; however, Complex partial seizures are frequently encountered. Stroke-like epi- sodes marked by transient hemiparesis or visual field deficits, diffi- cult to distinguish from postictal Todd's paresis, are described in SWS. However, the stroke-like episodes are more prolonged than a postictal paresis and may last days, weeks, or months, or become permanent. It has been suggested that SWS patients may have regional cerebral hypoperfusion with brain areas at risk for sustained ischaemia. Neuroimaging is of prognostic value since most children with facial port-wine stains without an intracranial involvement would develop normally. Plain radiographs of the skull, although now in- creasingly obsolete, may detect intracranial calcifications following the gyral patern, revealing the classic 'tram line' appearance; however, calcifications are often not present before age 2 yr. Brain MRI with gadolinium contrast demonstrates the presence of the leptomenin- geal angioma and involvement of other brain structures, if present (Fig. 24.17.11). CT of the brain reveals calcifications in the involved leptomeningeal vessels. Fig. 24.17.11 MRI and FDG PET images for a three-year-old boy with bilateral facial PWS, left sided hemiparesis and seizures;
(a). (b). axial and coronal T1 weighted MRI with gadolinium contrast respectively showing assymetric leptomeningeal enhancement, prominent choroidal vessels, and right-sided atrophy;
(c). FDG PET showing right-sided hypometabolism most prominent in the right frontal region.
Reprinted from European Journal of Paediatric Neurology 18(3), Sudarsanam A and Ardern-Holmes SL, Sturge–Weber syndrome: from the past to the present, pages 257–66, Copyright © 2014, with permission from Elsevier.

section 24 Neurological disorders 6208 No specific treatment exists for SWS. Port-wine stains can be treated by selective photothermolysis with a pulsed-dye laser. The best response to laser treatment occurs in smaller lesions and in younger children (<1 yr), probably related to development of ectasias in older children. Complications include scarring and transient hyperpigmentation. Ophthalmologic evaluation is es- sential in the neonatal period for assessment of congenital glau- coma; further recommendations are quarterly ophthalmologic evaluations for first two years of life followed by at least yearly evaluations if the examination remains normal. Glaucoma is treated with topical medications as indicated. Surgical therapy is required when the intraocular oressure does not normalize. Seizure management may be difficult in SWS. Management of seizures in SWS often is difficult and medical management may not always achieve adequate seizure control. Carbamazepine is the recommended antiepileptic of choice. In refractory cases, sur- gical options are hemispherectomy, or limited surgical resection of epileptogenic tissue. Cowden syndrome Cowden syndrome, or multiple hamartoma syndrome (MIM 158350), an autosomal dominant condition, is a subtype of PTEN hamartoma tumour syndrome. It manifests as multiple hamartomas in a variety of tissues along with dermatologic changes and an in- creased

risk of developing several types of systemic cancers at a young age. It has an estimated prevalence of 1 in 200 000 people. It is caused by more than 300 known mutations in the PTEN gene or phosphatase and tensin homologue, a tumour suppressor gene located on chromosome 10q23.3. Twenty-five to 34% of patients with Cowden syndrome have germline mutations in the PTEN (phosphatase and tensin) homologue gene that negatively regulates the PI3K/AKT/mTOR signalling pathway. Thus, loss of PTEN re- sults in activation of the pathway, which is critical in carcinogenesis. Germline mutations in PIK3CA and AKT1 have also been reported in patients with Cowden syndrome and in individuals without a germline PTEN mutation. Patients with Cowden syndrome usually present with mucocu taneous or extra-cutaneous hamartomatous tumours involving multiple organs along with an increased lifetime cumulative risk of developing breast cancer, thyroid cancer, endometrial cancer, colorectal cancer, renal cancer, and melanoma. Lhermitte-Duclos disease, now recognized as part of CD, is a very rare condition char- acterized by dysplastic gangliocytoma of the cerebellum known to present with headaches, cerebellar ataxia and cranial neuropathies, and may cause increased intracranial pressure. Management of Cowden syndrome is multifaceted, including periodic surveillance with screening for malignancies and treatment of benign and malignant manifestations with medical or surgical therapy. Although no therapies have been approved for patients with Cowden syndrome, clinical trials evaluating the role of PIK3CA/ mTOR inhibitors such as sirolimus are underway. Proteus and Proteus-like syndrome Proteus syndrome (MIM 176920) is a rare disorder comprising ir- regular, progressive postnatal overgrowth, and malformations of skin, connective tissue, fat, brain, and other tissues. Proteus syn- drome is associated, through a somatic activating mutation in the AKT1 oncogene, with AKT kinase activation, which regulates cell proliferation and apoptosis. Cutaneous capillary and venous mal- formations also occur. Proteus syndrome is also associated with monomorphic adenoma of the parotid glands and bilateral ovarian cystadenoma. Unilateral cystadenoma and meningioma have also been reported in patients with Proteus syndrome. Clinical recogni- tion and diagnosis is often difficult owing to overlap with other over- growth syndromes. The role of AKT inhibitors and mTOR inhibitors for the treatment of Proteus syndrome needs further exploration. Bannayan–Riley–Ruvalcaba syndrome Bannayan–Riley–Ruvalcaba syndrome (BRRS, MIM 153480) is one of the PTEN hamartoma tumour syndrome along with Cowden syndrome and Proteus-like syndrome. Germline mutations in the PTEN (phosphatase tensin) are found in two-thirds of individuals with BRRS; although autosomal dominant in nature, spontaneous mutations are also described. PTEN, a tumour-suppressor gene, has been mapped to chromosome 10q23.3. Mutations in the gene lead to unregulated proliferation of the three embryonic germ layer cells causing ectodermal, mesodermal, and endodermal hamartomas. This rare autosomal dominant disorder is characterized by macro- cephaly, intestinal hamartomatous polyps, lipomas, pigmented maculae of the glans penis, developmental delay, and intellectual im- pairment. Vascular malformations, such as arteriolovenous shunts, arteriovenous anomalies, and arteriovenous fistulas, are described in a subset of BRRS patients. Section II: Defects in DNA repair As in the phacomatoses, the diseases involving defects in DNA repair cause skin abnormalities, neurological manifestations, and tumours, although the tumours are outside the CNS. Xeroderma pigmentosum Xeroderma pigmentosum (XP) is a recessively inherited disorder with 100% penetrance and an estimated incidence of 1 in 100 000 to 1 in 1000 000. Eight different causative genes (XPA, XPB, XPC, XPD, XPE, XPF, or XPG) have been mapped, all of which are in- volved in either nucleotide excision repair or post-DNA replication translation synthesis. Mutations result in cellular hypersensitivity to the damaging effects of ultraviolet radiation (UV) resulting in a 10 000-fold increased risk of skin cancers. In the most severely af- fected form, the XP-A gene, mapped to chromosome 9q34.1, is de- fective. The protein

product of this gene has a much higher affinity for UV-damaged DNA than undamaged DNA, indicating a role for this protein in damage recognition. XP, defined by extreme sensitivity to sunlight, resulting in sun- burn, pigment changes in the skin, and a greatly elevated incidence of skin cancer, begins in childhood. Neurological manifestations occur in 20 to 30% of patients. Severely affected children are symp- tomatic at age of 2 years often with loss of reflexes as the initial sign ((De Santis–Cacchione syndrome). Further neurological deteri- oration causes progressive mental deterioration, cerebral atrophy, sensorineural deafness, choreoathetosis, cerebellar ataxia, periph- eral neuropathy, and growth retardation. Median age at death in XP patients with neurodegeneration (29 years) is significantly younger than those without neurodegeneration (37 years). Ocular signs are

 restricted to the anterior, UV-exposed structures of the eye (lids, cornea, and conjunctiva) and include photophobia, conjunctival erythema, keratitis, and tumours. Frequent dermatological evaluation, total protection from sun ex- posure and UV-emitting lamps is employed. Pre-malignant lesions are treated with cryotherapy, liquid nitrogen, topical 5-fluorouracil (5-FU) or topical imiquimod. Although there were significant side effects, oral isotretinoin is effective in decreasing the number of new nonmelanoma skin cancers. Early and adequate treatment of skin cancers is extremely important; all suspected tumours should be biopsied and removed. Ataxia-telangiectasia Ataxia-telangiectasia (MIM 208900) is an autosomal recessive dis- order is caused by mutations in the ATM (for AT mutated) gene located on chromosome 11q22–23. The gene product, which is ex- pressed in all tissues, encodes a large protein that is a member of the phosphatidylinositol-3 kinases that serve as a regulators of the cell cycle checkpoint in response to breaks in double-stranded DNA. Defective or missing product delays accumulation of the tumour- suppressor p53 in response to DNA damage, thereby increasing the risk for cancer. Cells are susceptible to damage by ionizing radi- ation or chemotherapeutic agents that cause double-stranded DNA breakages. Ataxia-telangiectasia (AT) presents in early childhood with un- steady gait and truncal instability. Infants’ meet major milestones until age 1; however, by age 2 to 3 years, staggering gait (ataxia) appears. Oculomotor apraxia (inability to follow an object to command) and dysarthria occur early but are difficult to evaluate in young children. Gaze initiation failure, choreoathetosis, and recurrent infections develop, followed by ocular telangiectasias between age 4 and 7 years. Later, cutaneous telangiectasias appear on the face, hands, and feet, the hair becomes prematurely grey, and lymph nodes are atrophic. Sexual infantilism, hepatic dys- function, and insulin-resistant diabetes develop in older patients. Speech becomes incomprehensible, mental functioning declines, and, by teens, the child has lost the ability to walk. Affected chil- dren generally become wheelchair bound by age 10 to 15 years. Cancer develops in 38%, mainly in the form of lymphoreticular tumours and acute T-cell leukaemias. Older patients develop epi- thelial tumours in various organs. There is also an increase in the incidence of cancer in heterozygotes, especially breast cancer in women. Death occurs in the second decade. Late-onset forms, with onset as late as third or fourth decade and milder phenotype, have been described. Laboratory tests reveal an elevated serum α-fetoprotein, low levels of IgA and IgG2, poor responsiveness to common antigens, and an increased sensitivity of the patient’s chromosomes to irradiation. On neuropathological examination there is a degeneration of the Purkinje and granule cells of the cerebellum, loss of anterior horn cells and dorsal root ganglion cells of the spinal cord, and loss of medullated fibres in peripheral nerves of some cases. General path- ology studies show absence or abnormal development of the thymus and all lymphoid system elements. Management of patients with ataxia-telangiectasia involves the

control of infections with antibiotics, monitoring for early signs of malignancy, the avoidance of multiple X-ray exposures, and the use of antitumour drugs rather than radiation therapy. Cockayne's syndrome Cockayne syndrome (CS, MIM 216400) is a progressive devastating multisystem disorder with a minimal incidence of 2.7 cases per million births, evaluated in Western Europe. Autosomal recessive mutations in ERCC6 (CSB) cause most (65%) cases of Cockayne syndrome whereas mutations in ERCC8 (CSA) account for the re- mainder (35%) cases. Both proteins are involved in DNA repair after ultraviolet damage and mutations lead to a specific cellular defect in transcription-coupled nucleotide excision repair. CS phenotypic spectrum ranges from 'classical' more severe type I; type II, overlapping with cerebral-oculo-facialskeletal syndrome (COFS); and a milder type III. Initially, COFS and UV-sensitive syn- drome were described independently from CS but eventually proved to be allelic to canonical Cockayne patients. Some rare patients show a very severe phenotype with combined features of CS and XP. In the classic form of this rare, autosomal recessive, multisystem, degenerative disease, symptoms start at the end of the first year or beginning of the second year. There is progressive growth failure and worsening post-natal microcephaly, constantly below three standard deviations in all forms of the disease. Psychomotor development is retarded with profound intellectual disability. Overall, the severity of the developmental delay is usually correlated with the overall severity of the disease. Loss of subcutaneous and orbital fat gives the characteristic facial appearance with enophthalmia. The face as- sumes a wizened, progeria-like appearance with sunken orbits, large beak-like nose, prominent ears, and narrow mouth and chin. The hair is sparse and the skin thin and photosensitive, but skin cancer does not occur. Eye signs include photophobia, decreased lacrima- tion, cataracts, retinal pigmentary degeneration, optic atrophy, stra- bismus, and nystagmus. Most CS patients show a unique combination of pyramidal, extra- pyramidal, cerebellar, and peripheral signs. Limb hypertonia and spasticity are early features associated with brisk of tendon reflexes. Almost all CS patients show cerebellar involvement with gait ataxia, action tremor, and dysarthria. Late-onset forms often present with cerebellar ataxia. Sensorineural deafness is a constant feature. Death occurs in the second or third decade. White matter loss and ventricle enlargement may be the earliest sign on brain imaging present in all clinical subtypes. Brain MRI shows progressive cerebral and cerebellar atrophy, brain calcifica- tions, and T2 white matter hyperintensities due to hypomyelination and in some cases secondary demyelination. Calcifications are seen in the basal ganglia, in the dentate nuclei and the subcortical white matter. There is no specific treatment for CS. Symptomatic management of neurological issues is provided as necessary. Section III: Metabolic disorders Leucodystrophies The term 'leucodystrophy' is generally applied to those diseases that have a genetic basis, a progressive clinical course, primary involve- ment of white matter, and a demonstrable/ presumed biochem- ical or molecular defect. In contrast, the leucoencephalopathies are those disorders of white matter that lack the genetic, progres- sive, or other qualities of the leucodystrophies, generally caused

 by acquired conditions such trauma, toxicity, or insult (e.g. peri- ventricular leukomalacia secondary to premature birth or white matter abnormalities caused by chemotherapy or meningitis). Most recent population-based estimate for leukodystrophies shows an incidence of 1 in 7500 live births; however, fewer than half of patients receive a specific diagnosis. Primary leucodystrophies are those inherited diseases with principal white matter involvement whereas, in secondary leucodystrophies, the involvement white matter is in associ- ation with other neurological structures and or organs and may lead to destruction of both axons and myelin by a more dif- fuse process. The primary leucodystrophies can be classified into three

subgroups: (1) classic dysmyelinative disorders (e.g. X-linked adrenoleukodystrophy, metachromatic leukodystrophy); (2) hypomyelinative with delayed or decreased myelin production (e.g. Pelizaeus–Merzbacher disease); and (3) vacuolating myelinopathies (e.g. Canavan's disease). Most vacuolating leocodystrophies lead to demyelination. Within the category of the secondary leucodystrophies are metabolic, mitochondrial, and muscular dystrophy, and various syndromic (genetic) disorders. Myelin development Myelin development requires complex developmental orchestration of genes, proteins, and different cell types such as oligodendrocytes, the glial cells that produce myelin and the myelin sheath, and inter- actions with other cell types, particularly neurons. It begins during fetal life and continues through adulthood. In addition to the pri- mary myelin function of accelerated action potential propagation, myelin is vital for maintenance of axonal health, and nutritional sup- port of axons. Oligodendrocytes or oligodendroglia arise from oligodendrocyte precursor cells during fetal and postnatal life. Each oligodendrocyte extends numerous myelin sheet-forming processes that envelope more than one axonal projection. Myelin, composed of proteins (30%) and lipids (70%), is produced in a highly energy-dependent manner. The most abundant protein components are myelin basic protein (MBP) and proteolipid protein (PLP). The lipid compo- nents of myelin are cholesterol, phospholipids, and glycolipids, mostly glycosphingolipids such as galactocerebrosides. Neuron- oligodendrocyte interactions are necessary for normal myelination and oligodendrocytes migration; extent of myelination is affected by neuronal activity. Myelination begins in the fourth month of gesta- tion with deep structures and proceeds in an inside–outside, dorsal- to-ventral, and caudal-to-rostral fashion. Essentially all areas of the brain are myelinated by the second year of life. Leucodystrophy could be caused by a large number of insults or processes that affect not only myelin development or myelin turn- over but also neurons or other glia such as astrocytes. On one hand, mutations in the intrinsic myelin protein PLP1 lead to Pelizaeus– Merzbacher disease, whereas mutations in the ubiquitously ex- pressed translation initiation factor subunits EIF2B1–5 cause vanishing white matter disease. Management A comprehensive team that includes specialists in neurology, physical medicine, orthopaedics, pulmonary medicine, and gastroenterology is often required to administer medical, social, and supportive care for most leukodystrophy patients and families. Medications may include antiepileptic drugs for seizures and medi- cations to reduce spasticity (baclofen, diazepam, tizanidine, botu- linum toxin). Proper physical therapy, exercise, and orthotics may be helpful in management of spasticity and gait disorder. Surgery may be indicated for contractures and scoliosis. Gastrostomy may be required in advanced disease to maintain nutrition in individ- uals who have severe dysphagia. Special education is usually ne- cessary for children with appropriate assistive communication devices. Genetic counselling is of utmost importance. Carrier status in parents, possibility of siblings being affected or carriers and risk of developing the disease in subsequent pregnancies should be expli- citly explained. Screening other family members for carrier state is recommended when making reproductive decisions. Classic dysmyelinative leucodystrophies Adrenoleucodystrophy X-linked adrenoleucodystrophy (X-ALD. MIM 300100), caused by a defect in the gene ABCD1, is the most common peroxisomal disorder with a pan-ethnic disease incidence of 1 in 20 000 males. ABCD1, which maps to Xq28, encodes for peroxisomal transporter ATP-binding cassette subfamily D member 1 (ABCD1, formerly ALDP) membrane protein that is a member of the ATP-binding cas- sette transporter superfamily. The protein mediates the import of very long-chain fatty acid (VLCFA) CoA esters across the peroxi- somal membrane. The dysfunction of ABCD1 results in impaired degradation of VLCFAs in peroxisomes. This leads to accumulation in all tissues and body fluids of saturated very-long-chain fatty acids (VLCFAs), particularly hexacosaenoic (C26:0) and tetracosaenoic (C24:0) acid. While

accumulation of VLCFAs is incriminated in the demyelinating pathology in AMN, the exact molecular mechanism by which VLCFAs are involved in the onset or progression of in- flammation in cerebral ALD is still not understood. Six-hundred and ninety-five (695) nonrecurrent mutations have been described in the X-ALD database, out of which 343 are missense mutations. Mutations such as deletions, frameshifts, and nonsense mutations generate truncated proteins; missense mutations often lead to un- stable proteins. Initially, de novo mutation rates of around 5% were described; however, recent studies report a higher de novo mutation rate of at least 19%. Pathologically, ballooning of cytoplasm with the presence of lamellar cytoplasmic inclusions is seen initially, most prominently in the zona fasciculata, followed by cytolytic cell death at a later stage. Although manifestations of X-ALD range from childhood to late adulthood, two predominant phenotypes are: adrenomyeloneuro pathy (AMN) and the cerebral form of X-ALD (CALD). CALD presents usually as childhood-onset condition, but occasionally adolescent-, and adult-onset, rapidly progressive cerebral form, are seen in affected males. AMN presents as adult-onset, slowly progres- sive myeloneuropathic form in males and upto 50% of carrier fe- males. Varying degrees of primary adrenal insufficiency (Addison's disease) are invariably found in affected males whereas this endo- crine disorder very rarely appears in females. Addison's only form is also known. The childhood cerebral form usually presents between 4 and 8 years of age, never before the age of 2.5 years, with behavioural

 symptoms. The child becomes withdrawn and less verbal, and has difficulty with auditory and visual discrimination. Spastic parapar- esis, incontinence, seizures, and feeding difficulties ensue with rapid progression to a vegetative state. Adults with adrenomyeloneuropathy (AMN) present with a slowly progressive paraparesis, together with sensory and sphincter disturbances. It is associated with a noninflammatory distal axonopathy involving the dorsal column and corticospinal tract in the lower thoracic and lumbar regions, as well as more proximal seg- ments of the corticospinal tracts in the internal capsule. In 30 to 40% of all male patients with AMN, there is inflammatory cerebral in- volvement detectable at the earlier stages of presentation or several years later. MRI often shows no abnormalities in the AMN pheno- type, apart from infrequent spinal cord atrophy and T2-weighted hyperintensity. Of males affected by X-ALD 70% have Addison's dis- ease, in most instances associated with cerebral ALD or AMN; how- ever, a smaller proportion of patients may have an 'Addison-only' phenotype of X-ALD, which is indistinguishable from Addison's disease attributable to other causes. Therefore, plasma VLCFA assay should be performed in all patients with idiopathic Addison's dis- ease, especially males. MRI of the brain in the childhood form shows a characteristic pattern of demyelination, found in approximately 80% of cases, involving confluent T2-weighted hyperintensity and Tl-weighted prolongation of the deep parieto-occipital white matter, which progresses in a centrifugal manner within a caudorostral direction (Fig. 24.17.12). There is gadolinium enhancement on T1-weighted imaging at the periphery of the involved white matter corres- ponding to regions of active demyelination and inflammation. A reverse pattern with frontal involvement is seen in another 15% of cases. Definitive diagnosis is established in males by demonstration of elevated levels of VLCFAs, which show abnormally high con- centrations of C26:0 as well as high ratios of C24:0 and C26:0 to C22:0. As the test results for VLCFAs may be falsely negative or equivocal in 10 to 15% of heterozygous women, mutation ana- lysis of the ABCD1 gene is recommended to confirm diagnosis or carrier state. Treatment includes general supportive care and symptomatic treatment for the patient. Adrenal hormone replacement therapy can be lifesaving; so all male patients should be adequately moni- tored for adrenal insufficiency. Haematopoietic stem cell transplant- ation (HSCT)

provides the most favourable outcome in children at the early stage of the illness with five-year survival rates of 92%, mortality rates of less than 5 % and a superior neurological and functional status compared with the group that have not received a transplant. Early stage is usually defined as a good clinical condition (e.g. performance IQ of 80 or higher) and few lesions on brain MRI (e.g. Loes score of 9 or less). Stabilization of the disease usually oc- curs about 6 months after the transplantation. Initially HSCT may accelerate the rate of progression, it is therefore, contraindicated in patients with advanced cerebral involvement. There is no disease-modifying treatment to prevent the onset or slow the progression of the chronic myelopathy of X-ALD. Lorenzo's oil, which is a 4:1 mixture of glyceryl trioleate and gly- ceryl trierucate, combined with moderate reduction of fat in the diet, normalizes or significantly lowers the levels of plasma VLCFAs, although it does not significantly alter the rate of progression in symptomatic individuals. Lorenzo's oil was proven to be ineffective in halting progression in several open-label trials; a placebo- controlled trial to determine if there is an effect on the rate of dis- ease progression was discontinued before completion and was not published. Lorenzo's oil may provide a preventive benefit in asymp- tomatic boys aged between 18 months and 8 years who are at the greatest risk for the development of the cerebral form of X-ALD and in whom the brain MRI is normal. Other approaches, including antioxidants are under investi- gation. Recently, transplantation with autologous bone marrow transfected in vitro with ABCD1 has been performed with success. A new method for newborn screening by determination of C26:0 lysophosphatidylcholine (C26:0-LPC) from dried blood spots may impact the detection, monitoring, and treatment of X-ALD. As X-ALD poses a significant burden to patients and families, pro- fessional genetic counselling is recommended. X-ALD heterozy- gous screening for women, together with prenatal diagnosis and preimplantation diagnosis, is available for families at risk. Fig. 24.17.12 (a) Brain MRI (axial images; FLAIR sequence) showing abnormally increased signal in the splenium of the corpus callosum, the parieto-occipital white matter, the visual pathways (optic radiations and lateral geniculate bodies), as well as the medial geniculate bodies of auditory pathway and the posterior limbs of the internal capsules. The demyelinating lesions are extensive and correspond to an advanced disease stage. (b) Brain MRI (axial images; FLAIR sequence) showing abnormally increased signal involving the posterior and anterior limbs
of the left and right internal capsule. Reprinted from Biochimica et Biophysica Acta 1822(9), Kemp S, Berger J and Aubourg P, X-linked adrenoleukodystrophy: clinical, metabolic, genetic and pathophysiological aspects, pages 1465–74, Copyright © 2012, with permission from Elsevier.

section 24 Neurological disorders 6212 Metachromatic leucodystrophy Metachromatic leucodystrophy (MLD, MIM 250100) is a sulphatide lipidosis caused by a deficiency of the lysosomal enzyme sulphatidase (arylsulphatase A, ASA), which catalyses the first step in the degradation of the sulphatide, 3-O-sulphogalactosyl- ceramide (cerebroside sulphate), or, in a few rare instances, a de- ficiency of cofactor saposin B (Sap-B). There is another distinct clinical form of ASA deficiency, multiple sulphatase deficiency, in which at least seven different sulphatases are defective due to an abnormality in their processing and functional maturation. MLD is an autosomal recessive disorder with an estimated frequency of 1 in 121 000, ranging between 1 in 40 000 and 1 in 300 000. Some genotypic–phenotypic correlation is possible: homozygosity of null alleles usually causes a late-infantile form of the disease, a combination of null allele and an allele with residual activity is as- sociated with juvenile onset, whereas two alleles with residual ac- tivity results in adult- or juvenile-onset disease. Deficiency of ASA results in the accumulation of the substrate, cerebroside sulphate forming lysosomal storage deposits, in the white matter of the CNS and

peripheral nervous system, which when stained with cresyl violet or toluidene blue reveal a brownish or reddish birefringence (metachromasia). Sulphatides are most abundant sphingolipids in myelin, accounting for 4% of its composition. Sulphatides accumu- late in the oligodendrocytes, Schwann cells, phagocytes, astrocytes, and also neurons. It has been shown in vitro that sulphatide loading triggers inflammatory cytokines involved in apoptosis. Exact mech- anism through which accumulation of sulphatides leads to demye- lination is not known. Most patients are equally divided between late-infantile and ju- venile onset, and about 20% of patients have an onset in adolescence or later. In the late-infantile form, the clinical signs begin between 15 months and 2 years, with frequent falls followed by the inability to walk, flaccid weakness, and peripheral neuropathy. The ability to sit without support is lost between 2 and 3 years of age. Speech becomes slow and indistinct, truncal titubation develops, optic atrophy be- comes apparent, and deep tendon reflexes are initially diminished and then lost. Spasticity develops in the legs but the arms remain hypotonic. Spinal root and peripheral nerve involvement cause ex- quisite sensitivity to touch. Electrophysiological testing shows slowing of the motor and sen- sory nerve conduction velocities. The cerebrospinal fluid protein level is elevated. Brain MRI T2-weighted images reveal centrifu- gally expanding, progressive, confluent, symmetrical white matter disease, with posteroanterior gradient. In the later stages of late- infantile MLD children are quadriplegic and spastic, with decere- brate, decorticate, or dystonic posturing, in association with loss of speech, seizures, hypertonic fits, bulbar palsy, and blindness. Death occurs 1–7 years after the onset of symptoms. Juvenile MLD presents between age 2.5 and 16 years, with poor school performance and gait imbalance, followed by confusion and inability to follow directions. The speech becomes slurred; spasticity and inability to walk ensue. Tremor, tonic spasms, and seizures may also occur. There is visual failure. Peripheral neuropathy is common but not invariable. Most patients with juvenile MLD do not live into adulthood. Adult MLD presents insidiously in late adolescence or early adult life with deterioration in school performance, disorganized thinking, poor memory, and a schizophrenia-like psychosis. The gait is ataxic with pyramidal signs such as hypertonia and hyperreflexia. Peripheral neuropathy may or may not be associated with the adult- onset variant of MLD. Incontinence can develop relatively early. Despite the presence of optic atrophy, vision, and the patient’s aware- ness of his or her environment are preserved until the end-stage of the disease. The progression is usually slower than in the early onset disease with spastic quadriparesis, decorticate posturing, and pathological reflexes noted after 5 to 10 years, but survival for several decades is possible. The widespread use of MRI, which shows pref- erential involvement of the subcortical white matter in the frontal regions in the adult-onset form, has improved recognition of this variant in psychiatric patients. Diagnosis is based on demonstration of low ASA activity levels in the peripheral blood leucocytes or skin fibroblasts. About 10% of the general population has a pseudodeficiency of ASA (i.e. low activity on testing in vitro due to the presence of a polymorphism but with no clinical neurological disease). This needs to be excluded before a conclusive diagnosis of MLD is made. Increased excretion of urinary sulphatides is indicative of true ASA deficiency, whereas urinary sulphatides are normal in pseudodeficiency. Similarly in saposin B deficiency, in vitro ASA levels may be normal as they are performed in the laboratory with water-soluble artificial substrate, but urinary sulphatide excretion is high. Brain MRI (Fig. 24.17.13) changes occur in the form of bilateral symmetric abnormal T2 signal hyperintensity starting in the corpus callosum and then involving the periventricular white matter. In the infantile form, the disease usually starts in the splenium of the corpus callosum and the parieto-occipital white matter, in the adult form, in the rostrum and frontal white matter. The subcortical fibres are usu- ally spared. With disease progression, there is involvement of the pro- jection fibres,

cerebellar white matter, basal ganglia and thalami with decreased signal intensity on T2-weighted images, probably as a result of accumulation of metal or other breakdown products in the brain. Typical for MLD the ‘tigroid pattern’ pattern which shows radiating stripes of normal signal intensity within the abnormal white matter. A scoring system based on MRI abnormalities combined with clinical parameters can be used as a measure of disease severity. Extent and severity of abnormal white matter signal, involvement of projection fibres, and basal ganglia atrophy is staged as mild, moderate, or se- vere. A low N-acetylasparate (NAA) level due to the diffuse neuronal loss and elevated myo-inositol due to to reactive gliosis characterize proton magnetic resonance spectroscopy (H MRS) in MLD. Progression of MLD may be slowed or halted when bone marrow transplantation or umbilical cord stem cell transplantation is under- taken in presymptomatic patients or early in the course of the dis- ease when neuropsychological signs are not advanced. Monocytic cells of bone marrow cross the blood–brain barrier then differentiate into microglial cells and deliver enzymes to oligodendrocytes and neurons to correct the enzyme deficiency. Since replacement of the resident microglia is slow, it can take 12–24 months until the dis- ease stabilizes. HSCT is therefore, ineffective for patients with overt neurological symptoms or for those with the aggressive infantile onset. In MLD, enzyme replacement therapy (ERT) administered intravenously is ineffective, due to the inability of the enzyme to cross the blood–brain barrier. Intracerebral agent delivery is cur- rently under investigation.

24.17 Inherited neurodegenerative diseases 6213 In gene therapy, the goal is to genetically modify autologous haematopoietic stem cells (HSC) to express or overexpress the ARSA gene. In a small study with three presymptomatic infantile MLD patients were treated with autologous HSCs transduced ex vivo with ARSA encoding lentiviruses and reinfused after the pa- tients had been treated with a myeloablative regimen. One year after reinfusion, functional ASA was isolated from cerebrospinal fluid and disease manifestation was halted for the follow-up times, ran- ging from 18 to 24 months. Multiple sulphatase deficiency (Austin’s disease) Mutations in SUMF1, which encodes a protein (the human C(α)- formylglycine-generating enzyme) involved in the processing of the catalytic site of all sulphatases, lead to a defective post-translational modification of several sulphatases and a neurovisceral disorder, mul- tiple sulphatase deficiency (MSD, MIM 272200). It is characterized by tissue accumulation of sulphatides, glycosaminoglycans (muco- polysaccharides), and cholesteryl sulphate. The clinical features of MSD overlap between the neurological findings of early infantile MLD and the dysmorphic facial features and skeletal deformities (i.e. dysostosis multiplex) seen with mucopolysaccharidosis (MPS). Urinary excretion of sulphatides, heparan sulphate, and dermatan sulphate is high. Clinical features include ichthyosis in young in- fants with psychomotor retardation, hepatosplenomegaly, deafness, and peripheral neuropathy. Diagnosis of MSD is based on charac- teristic clinical manifestations and demonstration of deficiencies of the arylsulphatases A, B (N-acetylgalactosamine-4-sulphate sulphatase), and C (steroid sulphatase), and four other sulphatases involved in the degradation of specific glycosaminoglycans. Globoid cell leucodystrophy (Krabbe disease) Collier and Greenfield described unusual ‘globoid’ cells in the white matter of patients with acute infantile diffuse ‘sclerosis’, a condi- tion reported initially in two siblings by Knud Haraldsen Krabbe, a Danish neurologist, in 1916. This condition, now termed Krabbe disease (MIM 245200), is caused by deficiency of galactocerebroside β-galactosidase (β-GALC; galactosylceramidase), which nor- mally cleaves galactosylceramide into ceramide and galactose. Pathologically, there is rapid destruction of myelin and myelin- forming cells (i.e. oligodendrocytes and Schwann cells) with Fig. 24.17.13 Axial T2 weighted (a, b, d, e, g, h) and sagittal T1-weighted (c, f, i) MR images of three patients with MLD. (a–c) A 2-year-old patient with

late-infantile MLD. Involvement of the periventricular white matter and centrum semiovale with parieto-occipital predominance and involvement of the splenium. U-fibres are spared. (d–f) A seven- year-old patient with juvenile MLD. (f) Shows the typical pattern of radiating stripes with bands of normal signal intensity in between. U-fibres are spared. (g–i): 28-year-old patient with adult MLD. In addition to the white matter signal abnormalities with frontal predominance, there is mild supratentorial atrophy (g, h). Reprinted from Best Practice & Research Clinical Endocrinology & Metabolism 29(2), van Rappard DF, Boelens JJ and Wolf NI, Metachromatic leukodystrophy: Disease spectrum and approaches for treatment, pages 261–73, Copyright © 2015, with permission from Elsevier.

section 24 Neurological disorders 6214 reactive astrocytic gliosis and tissue infiltration by multinucleated macrophages, that is, globoid cells filled with PAS (periodic acid– Schiff)-positive materials. Psychosine (galactosylsphingosine), a toxic metabolite that accumulates in the brain, is considered to be detrimental to the myelin-forming cells. Disease incidence in the general population is estimated at 1 in 100 000. There are at least 130 reported mutations in the β-GALC gene that cause Krabbe's disease. Eighty to 95% of known cases, present as an early infantile form, with onset between 3 and 6 months of life. They have marked irrit- ability, rapidly progressive generalized rigidity, and tonic spasms. Clenched fists and myoclonic jerks may be the earliest noted signs. Blindness and optic atrophy with pendular nystagmus develop later. The earliest objective findings in Krabbe disease are abnormalities of the brainstem auditory-evoked response (ABR) as well as the visual- evoked potential. Brain MRI shows symmetrical T2-weighted signal abnormalities in the periventricular region of the posterior cerebral hemispheres. Nerve conduction studies reveal markedly reduced nerve conduction velocities, while cerebrospinal fluid protein is ele- vated. Visceral organs as well as the skeletal system are unaffected. Death occurs between the ages of 1 and 2 years secondary to respira- tory difficulties and/or bronchopneumonia. About 10 to 15% of patients present with the late-infantile or juvenile form of the disease at approximately 5 years of age. They have a progressive gait disorder, spastic paraparesis, and cerebellar ataxia. Dystonia and visual failure may be associated. Behavioural changes and intellectual impairment may be the presenting features in juvenile-onset patients. The diagnosis of Krabbe disease is made based on deficient β- GALC activity in peripheral leucocytes or cultured skin fibroblasts. Gene sequencing further confirms the diagnosis. Mutation analysis is helpful for screening of siblings as well as other carriers in the family and prenatal diagnosis of any subsequent pregnancies. There is no definitive treatment for Krabbe disease. HSCT, using umbilical cord blood, is effective in modifying the clinical course and improving the neurological status of infantile Krabbe's disease; however, it is most effective if performed in the presymptomatic stages. Substrate reduction and chemical chaperone therapies are being considered. New-born screening (NBS) was instituted in the State of New York in United States in 2006. Early infantile variant has been detected in only 1:400 000 New York babies during the first 8 years of NBS, with late-onset variants being more frequent. The false-positive rate and positive predictive value of New York's MS/ MS-based enzyme assay, as reported in the Advisory Committee on Heritable Disorders in New borns and Children (ACHDNC) evidence review, were 0.004% and 8%, respectively. Several other states in the United States through legislative action have mandated newborn screening for lysosomal storage disorders. There are pilot projects undertaken in other states in the United States as well as across the world. Alexander disease Alexander disease (MIM 203450), a sporadic autosomal dominant condition first reported by WS Alexander in 1949, is an unusual form of leucodystrophy presenting clinically and pathologically with white matter dysfunction but caused

by mutations in the rod domain of the glial fibrillary acidic protein (GFAP) gene, resulting primarily in astrocytic dysfunction. A pathological hallmark of Alexander dis- ease is the presence in the astrocytes of eosinophilic, refractile, often rod-shaped, cytoplasmic inclusions termed ‘Rosenthal fibres’, which contain the intermediate filament protein GFAP in association with αβ-crystalline, small heat-shock proteins. These are predominantly distributed in the subependymal, subpial, and perivascular regions, in the basal ganglia and thalamus, and in the brainstem. There is widespread myelin deficiency in infantile cases associated frequently with cystic degeneration and cavitation. The arcuate fibres as well as occipital lobes and cerebellum are spared. In the juvenile-onset form, the white matter degenerates whereas adult-onset disease may have only patchy zones of myelin pallor or cavitation. The most common infantile form, with age of onset between birth and 2 years, is a relentlessly progressive lethal condition presenting as megalencephaly, seizures, hydrocephalus, and psychomotor re- tardation, and progressing to spastic quadriplegia. Survival varies from a few weeks to several years, but rarely beyond the early teens. Juvenile-onset Alexander disease between ages of 4 and 10 years presents with slowly progressive ataxia, spasticity, and bulbar signs, including speech and swallowing difficulties with relatively preserved intellect. Adult-onset presentation, increasingly recognized and no longer considered a very rare form of the disease, is often character- ized by pseudo-bulbar signs, ataxia, and spasticity, associated with atrophy of the medulla and upper cervical cord on neuroimaging. Clinical variability ranges from a presentation similar to juvenile- onset Alexander disease, progressive spastic paraplegia, slowly progressive dementia to relapsing–remitting neurological symp- toms mimicking multiple sclerosis that becomes recognizable as Alexander’s disease upon neuropathological examination. Recently, Alexander disease is divided into 2 groups: type I was characterized by early onset seizures, megalencephaly, and typical MRI features, and type II with a later age at onset characterized by brainstem fea- tures and atypical MRI findings. Classic MRI features for the infantile variant include frontal white matter changes, a periventricular rim with high T1 and low T2 signal and T2 hyperintensity involving the basal ganglia, thalamus, and brainstem (Fig. 24.17.14). There is contrast enhancement of peri- ventricular grey and white matter structures such as ventricular lining, periventricular rim of tissue, white matter of the frontal lobes, optic chiasm, fornix, basal ganglia, thalamus, dentate nu- cleus, and brainstem. Periventricular structures may appear swollen and cystic giving rise to a suspicion of tumour. Finding Rosenthal fibres on pathology may further complicate the issue. Atrophy and signal change of the medulla and spinal cord dominate in late-onset Alexander disease. Middle cerebellar peduncle abnormalities have been described. Alexander disease should be entertained in the dif- ferential diagnosis, especially in juvenile or adult cases, when brain MRI shows predominant or isolated involvement of posterior fossa structures, multifocal, tumour-like brainstem lesions and brainstem atrophy, diffuse signal changes involving the basal ganglia, thalamus, or both, with contrast enhancement, as well as a garland-like appear- ance of the ventricular wall. Management of patients with Alexander disease is symptomatic. Seizure management in children can be challenging. In late-onset cases, supportive measures include treatment for spasticity and aids for ambulation.

Pelizaeus–Merzbacher disease Pelizaeus–Merzbacher disease (PMD, MIM 312080), the proto- typical X-linked recessive hypomyelinating disorder, is caused by alterations in the proteolipid protein (PLP) gene (PLP), which in oligodentrocytes encodes two major CNS myelin proteins: PLP and its spliced isoform DM20. The phenotypic spectrum of PMD ranges from PMD type II (connatal form) to PMD type III (transitional form) to PMD type I (classic form) to spastic paraplegia type 2 (SPG2;

complicated form, to SPG2 (pure form), and is closely related to the genotype. Missense mutations in the highly conserved region of the DM20-related protein family cause the most severe forms, whereas Fig. 24.17.14 (a) Axial, (b) coronal, and (c) sagittal T2-weighted images show abnormally hyperintense white matter in both frontal lobes, with involvement of subcortical fibres. There also is a radial arrangement of hypointense stripes within abnormally hyperintense posterior white matter (arrows). Note the subcortical white matter is spared in these regions. (d) Magnified axial inversion recovery image shows details of the hypointense radial stripes (arrows), constituting a typical tigroid pattern. Note: Tigroid pattern on MRI: Tigroid pattern is evident on T2 weighted MR imaging. It is a peculiar arrangement of radially oriented T2-hypointense stripes within the abnormally hyperintense deep parieto-occipital white matter. The stripes are thought to represent relatively preserved perivascular myelin within the abnormal white matter. Although it was first reported in Pelizaeus–Merzbacher disease and it is considered to be a hallmark of metachromatic leukodystrophy (MLD) and globoid cell leukodystrophy (GLD). It is rarely described in other lysosomal storage disorders such as infantile GM1 gangliosidosis (GM1) and leukodystrophies such as Alexander disease. It is not invariably present in all affected patients. Reprinted with permission from Biancheri R et al. (2013) Magnetic Resonance Imaging ‘Tigroid Pattern’ in Alexander Disease. Neuropediatrics 44(3), 174–6, Copyright © 2013, Georg Thieme Verlag KG.

section 24 Neurological disorders 6216 substitutions of less conserved amino acids, as well as gene alterations that do not affect the DM20 isoform such as truncations, or dele- tions, cause less severe forms of PMD and SPG2. Large duplications including the entire PLP gene are the most frequently encountered mutations, which cause the classic phenotype; triplications cause a more severe phenotype. Seitelberger delineated the neuropatho- logical characteristics in PMD, which correlate well with the severity of the clinical presentation. The common pathological characteristics include lack or reduction of myelin sheaths in large areas of the white matter, with a patchy appearance of relatively conserved thin myelin islets, resulting in a ‘tigroid’ pattern. The structure of neurons and their processes including axons is well preserved. The typical early manifestations of classic PMD as described by Pelizaeus and Merzbacher, include hypotonia, nystagmus, and de- layed motor development within the first year of life, followed by spasticity, cerebellar dysfunction, dystonia, and choreoathetotic movements and then disappearance of the nystagmus. Seizures may or may not be present. Patients often show slow development in the first decade of life; up to 45% of patients may be able to assume a sitting posture and some may be able to walk and acquire language capabilities. Slow deterioration begins in the second decade until death in mid-adulthood. In the connatal form there is congenital psy- chomotor developmental arrest with feeding problems, stridor, and spasticity, leading to progressive contracture of extremities, often ac- companied by seizures. Death occurs in the first decade of life. Spastic paraplegia type 2 (SPG2) is allelic to PMD based on partial overlap of clinical manifestations with PMD and the discovery of PLP1 mutations in SPG2. In SPG2 normal motor development oc- curs in the first year of life, but progressive weakness and spasticity of the lower limbs develop between the ages of 2 and 10. In addition some clinical features seen in PMD, such as nystagmus, optic at- rophy, ataxia, dysarthria, and intellectual impairment, although less prominent, may be present. Later-onset spastic diplegia with no add- itional neurological complications (the pure form of SPG2) has also been reported. Most female carriers of PLP mutations are asymp- tomatic; however, in rare families, including the family described by Pelizaeus, manifestations ranging from mild spastic diplegia to pro- gressive leucodystrophy with dementia have been reported. Female carriers for PLP mutations causing a mild phenotype in males tend to be symptomatic, whereas those carrying

mutations causing severe phenotypes in males are usually asymptomatic in female carriers. This may be related to a skewed pattern of X inactivation in cells in which a severe mutation favours preferential inactivation whereas a milder mutation may not confer the selectivity or to the elimination of oligodendrocytes expressing severe mutations during early mye- lination, unlike those expressing milder mutations that persist. The fact that PMD is characterized by delay in myelination and not by demyelination is reflected in T2-weighted images on brain MRI as diffuse hyperintensity, which typically involves all the white matter including cerebral hemispheres, cerebellum, and brainstem, unlike many other demyelinating leucodystrophies, where abnormalities are often confined to specific regions (Fig. 24.17.15). Additionally, T1-weighted signals from white matter in PMD are usually normal or isointense, unlike other demyelinating or dysmyelinating con- ditions where the T1 signal is hypointense. Thinning of the corpus callosum and atrophy of the cerebral hemispheres may be seen in se- vere PMD cases. Sparing of the corticospinal tracts can occur in clas- sical PMD. Patients with the PLP null phenotype have milder diffuse abnormalities of the white matter whereas milder SPG2 phenotype may have patchy areas of hypomyelination on MRI. Definite MRI abnormalities may not be apparent until age two. Extensive but non- progressive abnormalities of multimodal evoked potentials are ob- served in PMD. Electromyogram and nerve conduction studies are normal. Diagnosis of PMD/SPG2 is made based on clinical presentation, X-linked inheritance pattern, MRI indicative of hypomyelination, and molecular testing confirming duplication or other mutation of the PLP1 gene. Currently, there is no definitive therapy for PMD. Symptomatic management of spasticity, feeding difficulties, and dystonia is recommended. 18q− syndrome 18q− syndrome, one of the most common chromosomal deletion syndromes, was first described by DeGrouchy in 1964. The clinical picture is distinguished by several dysmorphic features including short stature, microcephaly, midface hypoplasia, malformed ears, stenotic ear canals, flat philtrum, carp-shaped mouth, prognathism, tapered fingers, proximal thumbs, and prominent fingerprint whirls, as well as numerous neurological deficiencies such as hypotonia, hearing loss, nystagmus, and intellectual impairment. The deleted 2-Mb region of 18q22–23 contains seven known genes, one of which Fig. 24.17.15 Brain magnetic resonance images of a two-year-old boy with PLP1 deletion. (a) T1-weighted axonal images are nearly normal. (b) T2-weighted axonal images show diffuse hypomyelination with some myelination still present in the posterior limbs of the internal capsule, corpus callosum, brainstem, and cerebellar peduncles. Reprinted from Brain and Development 34(10), Torisu H et al., Clinical and genetic characterization of a 2-year-old boy with complete PLP1 deletion, pages 852–6, Copyright © 2012 The Japanese Society of Child Neurology, with permission from Elsevier.

 encodes for myelin basic protein (MBP), which is a key structural protein of CNS myelin. As the deletion most often involves the distal portion of the long arm of chromosome 18 from q21 to qter, haploinsufficiency of MBP is implicated in the delayed or incom- plete development of myelin seen on brain MRI; however, proton MR spectroscopy (MRS) studies suggest the possibility of active de- myelination or increased myelin turnover. The characteristic pattern of dysmyelination on brain MRI T2-weighted images, which shows low grey matter–white matter contrast, persists in individuals with 18q– beyond their first decade. The severity of dysmyelination ap- pears to correlate with the severity of other features of the 18q syn- drome, implicating the role of other deleted genes more proximal to the MBP locus in defective myelination in these patients. Pelizaeus–Merzbacher-like disease Uhlenberg et al. in 2004 reported children with Pelizaeus– Merzbacher-like disease (PMLD) with mutations in GJA12 (gap junction protein, α-12 gene), now known as gap junction pro- tein, γ-2 gene (GJC2, MIM

608803). Only 8% of PMLD cases are caused by mutations in GJC2. GJC2 encodes a member of a large family of connexin proteins, called connexin 47 (Cx47) or connexin 46.6 (Cx46.6), which is a 4-pass transmembrane protein highly ex- pressed in oligodendrocytes. PMLD caused by GJC2 mutations, called PMLD1 (MIM 608804), or leukodystrophy hypomyelinating 2 (HDL2), has an autosomal recessive mode of inheritance with missense, nonsense, frameshift, and indel mutations reported. Patients with PMLD and GJA12 mutations show the character- istic clinical symptoms such as nystagmus and impaired motor development in infancy, followed by ataxia, choreoathetotic move- ments, dysarthria, and progressive spasticity. Up to 70% of these patients have been reported to acquire walking capability; their intellectual functions were well preserved compared with their motor impairment. Epileptic seizures and peripheral neuropathy have been reported in a few cases. In patients with GJA12 pro- gression of mutations is slower, their cognition is better preserved, and there is partial myelination of pyramidal tracts compared with classic PMD. Brain MRI is similar to that of PMD with high T2-weighted signal throughout the cerebral white matter and pyr- amidal tracts. Severe hypomyelination associated with increased N- acetylaspartylglutamate in the cerebrospinal fluid. A rare disorder that must be considered in the differential diag- nosis of connatal forms of PMD has been reported in two unrelated girls with almost complete absence of myelin on cerebral MRI, as shown by a homogeneous high signal of white matter on T2-weighted images and a low signal on T1-weighted images in association with highly elevated concentrations of N-acetylaspartylglutamate (NAAG) in their cerebrospinal fluid. Clinical features include |rota- tory nystagmus within the first 2 months, epilepsy, feeding difficulty, and acquired microcephaly. Initial pyramidal signs were followed by hypotonia and loss of reflexes secondary to peripheral neuropathy. No mutation could be found in the gene encoding the NAAG- degrading enzyme. No further reports have appeared in literarture since first description in 2004. Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) In 2002, van der Knaap et al. described seven unrelated patients with unidentified leucodystrophy. MRI picture was characteristic of diffuse myelin deficiency in the central white matter and at- rophy of the neostriatum (caudate and putamen) and cerebellum (vermis greater than hemispheres). This condition was labelled as hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC). Subsequently these cased were found to have a heterozy- gous c.745G. A mutation in TUBB4A, encoding for tubulin β 4A. At least 23 additional patients have been described. Presenting fea- tures are usually motor in the form of oculomotor symptoms, speech complaints, gait instability, or hypotonia. All patients had spasticity and majority had ataxia, movement disorder choreoathetosis or dystonia, rigidity, and dysarthria. Two thirds of patients described thus far are male, two thirds had symptom onset before age 2 and two thirds had delayed motor development. Half of the patients had tremors, microcephaly, and short stature. On MRI, there was diffuse myelin deficiency with high signal intensity on T2-weighted images in the cerebral white matter including the corpus callosum, internal capsule, and pyramidal tracts in the midbrain and pons. With pro- gression of the disease there was dilatation of the lateral ventricles and atrophy of the caudate nucleus, putamen, and cerebellum. Hypomyelination and congenital cataract Hypomyelination and congenital cataract is a rare autosomal re- cessive hypomyelinating leucodystrophy, described by Zara et al. in 2006, caused by deficiency of hyccin, a membrane protein implicated in both central and peripheral myelination. The FAM126A gene lo- cated on chromosome 7p21.3-p15.3 encodes it. Other features are progressive neurological impairment and congenital cataract. Most patients have cataract surgery within their first few months and in- tellectual impairment and developmental delay are evident by 1 year. Almost all achieve the ability to walk in the second year with support but lose this ability by the end of first decade to become wheel chair bound due to slowly progressive

pyramidal and cerebellar dysfunc- tion, as well as peripheral neuropathy manifesting as lower-limb muscle weakness and wasting. Neurological findings include dys- arthria, truncal hypotonia, brisk tendon reflexes, and bilateral ex- tensor plantar responses along with cerebellar signs, such as truncal titubation and intention tremor. Recently milder phenotypes have been described. Subsequent studies have described milder pheno- types such as delayed cataract and ability to walk without support. Brain MRI shows diffuse cerebral hypomyelination with increased white matter water content and progressive white matter atrophy with preservation of the cortex and deep grey matter structures. Electrophysiological studies show evidence of demyelination as well as axonal pathology in most patients. 4H (hypomyelination, hypodontia, hypogonadotropic hypogonadism) leukodystrophy/ Leucoencephalopathy with ataxia, hypodontia, and hypomyelination Wolf et al. in 2005 described four patients with early onset progres- sive ataxia, short stature, and a distinctive pattern of hypodontia, hypomyelination, and cerebellar atrophy with ataxia. Motor devel- opment was normal or slightly delayed and mental development was mildly retarded. Four adult patients with milder neurologic signs and hypogonadotropic hypogonadism were described shortly there- after. Subsequently, mutations in POLR3A, coding for the largest subunit of RNA polymerase III and POLR3B, encoding another sub- unit of this polymerase, have shown to cause 4H, as well as 2 other entities: ‘hypomyelination with cerebellar atrophy and hypoplasia

section 24 Neurological disorders 6218 of the corpus callosum’, and ‘leukodystrophy with oligodontia’. In general, patients with POLR3A mutations are more severely affected than patients with POLR3Bmutations with faster regression and shorter life expectancy. 4H leukodystrophy has a spectrum of disease severity. At the se- vere end, affected children do not achieve independent walking and have mild-to-moderate intellectual disability. At the milder end of the spectrum, patients present after age 5 years with learning diffi- culties and motor clumsiness. About 10% cases present late, after age 10 years. Developmental delay is noted in half the patients between the age of 1 and 2 years. Unsupported walking if achieved was usu- ally before age 2 years; about a fifth are never able to walk independ- ently. Majority of patients have severe intention tremor, dysmetria and/or gait ataxia. Abnormal smooth pursuit and gaze-evoked nys- tagmus is present in most patients. Speech and swallow deteriorate slowly as well. Epilepsy, pyramidal signs and extrapyramidal signs, including dystonia, are less common. Wheelchair dependence oc- curs by the end of the first decade, but several patients may still be ambulatory in adulthood. Learning difficulties or mild-to-moderate intellectual disability in present in most. Cognition usually deteri- orates slowly in the second decade. Acute neurologic deterioration with infections is known with not all children regaining their pre- vious level. Hypodontia and dental abnormalities are prominent with natal teeth, delayed dentition with abnormal order of deciduous tooth eruption and upper median incisors erupting late or not at all. However, dental abnormalities may be seen only in two thirds of pa- tients and as such are not required to make the diagnosis. Delayed puberty secondary to hypogonadotrophic hypogonadism, is seen in three fourths of cases. Growth hormone deficiency is also reported in some patients. Another noteworthy feature is pronounced and progressive myopia. Pathological examination in one case of a 14-year-old girl showed diffuse white matter atrophy with thin corpus callosum, enlarged lateral ventricles, and nonhomogeneous discoloration of the white matter. Histologic analysis revealed variable white matter rarefac- tion, lack of myelin, and reduced numbers of oligodendrocytes with better preservation of the perivascular myelin in the centrum semiovale. Foamy macrophages were seen clustering around small blood vessels. The cerebellar folia were mildly atrophic and there was nonhomogeneous lack of myelin in the deeper

cerebellar white matter. Brain MRI invariably showed hypomyelination (i.e. T2- weighted images show a diffusely hyperintense signal and a normal hyperintense signal on T1-weighted images with myelination of the optic radiation and small T2 hypointense dot in the posterior limb of the internal capsule). A thin corpus callosum is evident by adult- hood. Cerebellar atrophy, particularly in the vermis, is also noted. Vacuolating leucoencephalopathies Canavan's disease Canavan's disease, an autosomal recessive disorder caused by defi- ciency of aspartoacylase, leads to a build-up of NAA in the brain, as well as to NAA acidaemia and NAA aciduria. Canavan's disease is pan-ethnic but there is a high prevalence of the carrier state, es- timated at 1 in 37 to 1 in 50, in the Ashkenazi Jewish community. Two point mutations (at positions 693C and 854A in the coding sequence) are responsible for 97% of mutant alleles in Ashkenazi Jews, whereas C914A is the most common mutation among non- Jews, found in 30–60% of mutant alleles. Aspartoacylase, a zinc carboxypeptidase enzyme expressed exclusively in the CNS in oligodendrocytes, normally hydrolyses NAA, which is derived from neurons to aspartic acid and acetate. The free acetate moiety is con- verted to acetyl-CoA by acetyl-CoA synthetase and presumably further utilized as a building block for myelin lipids. Pathologically, intermyelinic oedema, widespread vacuolation in the lower layers of the cerebral cortex, and subcortical white matter and lack of myelin occur, along with astrocytic swelling and mitochondrial changes re- sulting in spongy degeneration of the brain white matter. Most cases present early in infancy but a few milder cases with a later onset have been encountered. Three clinically distinct groups of Canavan disease have been identified: (i) the congenital form with severe symptoms in the first few weeks of life; (ii) the infantile form, the most common form in which the disease is apparent by 6 months of age; and (iii) the juvenile form, in which the disease is apparent by the age of 4 or 5 years. Infants with Canavan's dis- ease appear normal at birth, but developmental delay and hypo- tonia, including head lag, are evident between 2 and 6 months of age followed by macrocephaly and severe impairment of motor development by 1 year. Other features include ataxia, inadequate visual tracking, and poor sucking ability. Optic atrophy, spasticity, and seizures soon ensue. In spite of profound delays, Canavan dis- ease patients can sometimes interact with others, smile, and reach for objects. Eventually, affected children become increasingly de- bilitated with age, and unable to move voluntarily or to swallow. Death typically occurs before adolescence. Mild/juvenile Canavan disease can go unrecognized due to mild phenotype and normal head circumference. Urine organic acid screen showing elevation of urine NAA, often more than 100-fold compared to normal individuals, is often the first diagnostic clue in evaluation of patients with Canavan's dis- ease. Diffuse loss of white matter including the subcortical U-fibres, which are usually spared in most other forms of leucodystrophy, is evident on brain MRI. There is a marked increase in the NAA peak in brain white matter on MRS. The deficiency in aspartoacylase ac- tivity can be confirmed in cultured skin fibroblasts from patients but enzyme determinations in cultured amniotic fluid cells are not reliable. Although not required for diagnosis, gene sequencing will reveal pathogenic mutations; this provides the necessary genetic in- formation for pre-natal testing of subsequent pregnancies. Calcium acetate has been tried in Canavan's disease to replace the deficient acetate and acetazolamide has been used to slow the pace of macrocephaly (Fig. 24.17.16). A long-term follow-up of gene therapy with an adeno-associated viral (AAV) vector carrying the ASPA gene (AAV2-ASPA) in 13 Canavan disease patients re- ported that the gene therapy was tolerable, no severe long-term ad- verse effects were noted, elevated NAA in the brain was reduced, the progression of brain atrophy was slowed, and improvements were observed in the frequency of seizures. Moreover, neurological examination showed significant improvement in motor functions in younger cohorts of treated CD patients, indicating the possible advantage of early therapeutic interventions. Prevention strategies have

included testing for carriers in Ashkenazi Jewish couples and prenatal diagnosis in at-risk pregnancies using NAA quantification in amniotic fluid and molecular analyses of chorionic villous cells and amniocytes.

24.17 Inherited neurodegenerative diseases 6219 Megalencephalic leucoencephalopathy with subcortical cysts Megalencephalic leucoencephalopathy with subcortical cysts (MLSC) is an autosomal recessive disorder caused by alteration in the gene MLC1, mapped to chromosome 22qtel, which encodes a membrane protein that is expressed almost exclusively in the brain, especially in astrocytes, and leucocytes. Based on the pattern of localization it is speculated that the MLC1 protein is involved in astrocytic regulation and/or transport of ions or other substances. MLC1 mutations all disrupt the membrane localization of the MLC1 protein. Mutations in HEPACAM, coding for hepatic and glial cell adhesion molecule GlialCAM, also cause MLC. GLIALCAM mutations also disrupt the localization of MLC1 indicating that MLC1 is central in the pathophysiology of MLC. At least 50 mu- tations have been found thus far in MLC1; however, members of the Agarwal ethnic group of northern India, in whom the disease is more prevalent, share a common homozygous mutation, 320insC, suggesting a founder effect. Histopathology shows a spongiform leucoencephalopathy in the subcortical white matter without cor- tical involvement. The outermost lamellae of myelin sheaths contain countless vacuoles with sparing the middle or inner parts of myelin sheaths. Although most vacuoles are covered by single myelin la- mellae, some vacuoles were partially covered by multi-lamellar myelin sheaths or oligodendroglial cell extensions. MLSC is characterized clinically by macrocephaly noted within the first year or at birth, slow progressive decline in motor functions including ataxia and spastic paraparesis several years later, leading to inability to walk, and seizures in about 60% of patients. Cognitive functions are only mildly impaired with some decline in the second decade. Characteristic MRI findings that distinguish MLSC from other megalencephalic leucodystrophies include diffusely abnormal and swollen cortical cerebral white matter and bilateral cystic changes, the appearance of which resembles that of cerebrospinal fluid in all sequences, especially in the temporal lobes, occasionally in the frontoparietal regions but sparing the occipital lobes. In addition, the cerebellar white matter may exhibit mildly abnormal T2 signal but there is no swelling. Eventually the swelling resolves and cortical atrophy de- velops. The number and size of the cysts progressively increase, such that they eventually occupy a significant portion of the frontoparietal cortex. The EEG shows multifocal epileptiform discharges. Supportive treatment, including treatment of seizures, is recommended. Vanishing white-matter disease (childhood ataxia with CNS hypomyelination) Childhood ataxia with CNS hypomyelination (CACH), a pan- ethnic autosomal recessive disease, also described as vanishing white matter disease (VWM) or myelinopathia centralis diffusa, was first identified in 1997. Astute application of molecular genetics in a population of a limited geographical region in the eastern part of the Netherlands led to the discovery that mutations in any one of the five subunits of eukaryotic translation initiation factor 2B (eIF2B) cause CACH/VWM and the recognition of a wider clinical spec- trum. The eIF2B protein complex has a key regulatory role in protein synthesis through initiation of translation. Regulation of the activity of eIF2 is a protective mechanism for cells in response to stress. Mutated eIF2B could impair the ability of cells to regulate protein synthesis, resulting in increased susceptibility to various physio- logical stress conditions. On gross examination of the brain, the cor- tical grey matter is of normal consistency in marked contrast to the white matter of the centrum semiovale which is softened, atrophic, and gelatinous. There is rarefaction with moderate-to-severe vacu- olation of the white matter with relative sparing of axons and sub- cortical U-fibres. The distinguishing feature of CACH/VWM is the

presence of foamy oligodendrocytes, which on ultrastructural ana- lysis show abnormal abundant cytoplasm containing membranous (a) (b) 1 2 Fig. 24.17.16 (a) T2 weighted image of MRI brain showing 1 characteristic symmetric white matter hyperintensities of subcortical U-fibres, and 2 symmetric white matter hyperintensities of brainstem and cerebellum. (b) Magnetic resonance spectroscopy showing a high peak of N-acetyl aspartate which is the characteristic feature of Canavan disease. Reprinted from Sreenivasan P and Purushothaman KK. Radiological Clue to Diagnosis of Canavan Disease. Indian J Pediatr (2013) 80: 75, Copyright © 2012, Dr K C Chaudhuri Foundation, with permission of Springer.

section 24 Neurological disorders 6220 structures and numerically increased and morphologically ab- normal mitochondria. Abnormally shaped coarse astrocytes and gliosis are present. In the severe forms, there is a reduction of the number of astrocytes and possibly astrocyte progenitors, but not of oligodendrocyte progenitors. Clinically, early development and head circumference are normal, while some patients may present with speech and cognitive delay. The most common initial presentation is new-onset ataxia between ages of one and five years. The disorder may be heralded by coma or a dysmetric tremor following mild head trauma or a febrile illness and apparently, even after an acute fright, can occur spontaneously. Subsequent deterioration is generally progressive with gait diffi- culty, cerebellar signs, pyramidal signs, dysarthria, and seizures. The course is often remitting–relapsing and patients may remain stable for years at any phase of the illness. Dysphagia and optic atrophy are seen late in the disease; the peripheral nervous system is usually un- affected. Death typically occurs during the first or second decade of life. There is a wide phenotypic spectrum which includes congenital forms with manifestations in organs besides the brain, a rapidly as well as a subacutely fatal infantile form, a slowly progressive form with onset after age 5 years that is often associated with ovarian insuf- ficiency (dysgenesis), termed ‘ovarioleucodystrophy syndrome’, and an adult-onset disease variant. Brain MRI shows symmetrically and diffusely abnormal subcortical white matter with hypointense signal on T1-weighted MRI and hyperintense signal intensity on T2 im- ages with sparing of the cortex. Cystic degeneration with a radiating stripe-like pattern or cavitation within the white matter is best seen on proton density or FLAIR sequences; there is no gadolinium en- hancement of these lesions on post-contrast T1-weighted MRI. Early and selective involvement of the inner rim of the corpus callosum (septo-callosal surface) is recently described as a distinguishing sign from other leucodystrophies. Supportive management such as avoidance of stress situations, use of antipyretics and antibiotics, physical therapy for motor dis- abilities, and carbamazepine for seizures is recommended. In fam- ilies with a known mutation prenatal diagnosis can be offered. Progressive cavitatory leucoencephalopathy Progressive cavitatory leucoencephalopathy (PCL) was initially reported in 2005 by Naidu et al. as childhood-onset progressive cavitatory leucoencephalopathy associated with an increase in lactate in brain, blood, and cerebrospinal fluid. There may be subtle devel- opmental delay followed by acute onset of irritability or neurological deficits occurring after 2 years of age, followed by steady or intermit- tent clinical deterioration with death between 11 months and 14 years of life. Brain MRI shows irregular asymmetrical patchy areas of white matter abnormality that evolved to multicystic degeneration. MRS shows elevated lactate in the affected structures. PCL appears to be a distinct genetic entity, possibly involving mitochondrial dysfunction, but the exact molecular basis is yet to be elucidated. Secondary inherited leucoencephalopathies Amino acidaemias Neurological manifestations including leucoencephalopathy are frequently present in the amino and organic acidaemias. MSUD is an autosomal recessive disorder caused by deficiency in a sub- unit of the branched-chain α-ketoacid

dehydrogenase complex, which is required for the oxidative decarboxylation of branched- chain ketoacids. MSUD-associated metabolites initiate a process leading to the proteolytic degradation of myelin proteins, thereby producing abnormal myelin sheaths. Patients with MSUD after a relaxed treatment protocol were reported to have myelin abnormal- ities demonstrated on T2-weighted brain MRI as increased signal in the mesencephalon and/or brainstem (cerebral peduncles and dorsal brainstem), less so in the basal ganglia–thalamus and globus pallidus, and less prominent areas of decreased signal intensity in T1- weighted images. More severely involved patients had supratentorial changes, especially in the occipital periventricular and cerebellar white matter. The myelin abnormality may be due to chronic ex- posure of the brain to branched-chain amino acids or to a deficit of essential large neutral amino acids, the transport of which across the blood–brain barrier is impaired by an excess of the branched-chain amino acids. In phenylketonuria (PKU), white matter changes on MRI are typ- ical of the adolescent and adult with PKU. However, the distribution of MRI signal abnormality is most marked in supratentorial regions and only in more severe cases does it extend into the basal ganglia, brainstem, or cerebellum. Organic acidaemias Cerebral MRI has revealed bilateral white matter changes in sev- eral organic acidopathies, including l-2-hydroxyglutaric aciduria, 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency, and 3- hydroxy-3-methylglutaryl-CoA lyase deficiency. Glutaric aciduria type 1 Glutaric aciduria type 1 (GA1) is an autosomal recessive disorder due to a deficiency of mitochondrial enzyme glutaryl-CoA dehydro- genase (GCDH) resulting in the accumulation of glutaric acid and 3-hydroxyglutaric acid in the blood, urine, and CSF. Macrocephaly is present at birth or within the first few weeks of life. Most chil- dren present with an acute encephalopathic crisis between 3 and 24 months of age in the setting of an infection or illness with de- hydration. Early myelinating tracts are usually spared white matter changes in GA1 primarily involve the periventricular white matter. Other characteristic MRI findings of GA1 include widening of the Sylvian fissure, decreased opercularization of the insula, and acute striatal necrosis. L-2-Hydroxyglutaric Aciduria L-2-hydroxyglutaric aciduria is caused by mutations in both alleles of the L2HDGH gene resulting in deficiency of L-2-hydroxyglutarate dehydrogenase, which is FAD-linked mitochondrial enzyme that converts L-2 hydroxyglutarate to α-ketoglutarate. Clinically, L-2 hydroxyglutaric aciduria presents with variable degrees of psy- chomotor and speech delay followed by a slowly progressive neurodegenerative disorder presenting as cerebellar, pryamidal, and extrapyramidal signs with cognitive decline. MRI findings are char- acteristic showing initial patchy and eventual confluent low signal on T1-weighted images and increased signal on T2-weighted images in the subcortical white matter bilaterally with frontal predomin- ance. Cerebellar and brainstem white matter is not involved.

24.17 Inherited neurodegenerative diseases 6221 Methylmalonic aciduria MMA is a heterogeneous autosomal recessive group of disorders characterized by accumulation of methylmalonic acid due to a de- fect in intracellular cobalamin metabolism (coenzyme deficiency). MMA typically presents fairly early in infancy with a history of poor feeding, vomiting, progressive lethargy, floppiness, and muscular weakness. Brain MRI scan typically demonstrate involvement of basal ganglia and white matter with the globus pallidus being se- lectively affected. Demyelination of corticospinal tracts in a pattern that resembles B12 deficiency of combined systems degeneration is also seen. Glycogen storage disease type IV/adult polyglucosan body storage disease Glycogen storage disease type IV (GSD IV), an autosomal recessive disorder, results from deficient activity of the branching enzyme 1,4-glucan-6-glucosyltransferase mapped to chromosome 3p14. It presents in infancy with severe liver disease, causing cirrhosis, portal hypertension, and early death. A fatal neonatal

neuromuscular form and a milder nonprogressive hepatic form are known. A late-onset variant, referred to as adult polyglucosan storage disease (APBD), first described in 1971. There is a predilection for Ashkenazi Jesish ancestry, although it has been described in all eth- nicities. Not all patients with APBD have deficiency of the glycogen- branching enzyme; however, when present levels are reduced to less than 25% of normal. ABD is characterized by onset in by the fifth of neurogenic bladder, which may precede other symptoms by a decade. Neurogenic bladder, spastic paraplegia, and axonal neuropathy are cardinal signs of the disease and present in 90% of the patients. Cognitive decline consisting of mild attention and memory deficit may also affect up to 50% of patients with APBD. Neurophysiological studies reveal an axonal sensorimotor peripheral neuropathy. The MRI shows extensive, nonenhancing, bilateral, symmetrical, peri- ventricular and subcortical white matter changes with the T2 signal abnormality extending to the posterior limb of internal capsule, external capsule caudally to pons and cervicomedullary junction, involving usually in the pyramidal tracts and the medial lemniscus. There is consistent and progressive atrophy of the brainstem (me- dulla) and spinal cord. Sural nerve biopsy, which can be diagnostic, shows frequent enlargements of myelinated fibres that stain posi- tive with PAS. PAS-positive inclusions are also found within skeletal muscle fibres and the apocrine gland cells of the skin.
Sjögren–Larsson syndrome Sjögren–Larsson syndrome (SLS) is an autosomal recessive dis- order resulting from mutations in the gene for the microsomal enzyme fatty aldehyde dehydrogenase (FALDH), first described in 1957 by Sjögren and Larsson in a consanguineous cohort of 28 patients from the county of Vasterbotten in northern Sweden. The worldwide prevalence of this pan-ethnic disorder is probably less than 0.4 per 100 000. FALDH catalyses the oxidation of medium- and long-chain fatty aldehydes to the corresponding carboxylic acids. Deficiency in FALDH leads to elevation of free fatty alcohols in the plasma and leukotriene B4 (LTB4) in the urine. The accu- mulation of fatty alcohols or aldehyde-modified marcromolecules disrupts the integrity of multilamellar membranes in skin and myelin. Neuropathologically, there is reduction in myelinated nerve fibres in cerebral and cerebellar white matter, loss of neurons in the cortex and basal ganglia, and deposition of pigments. PAS- positive lipoid substances are found in the subpial, subependymal, and perivascular glial layers as well as in cerebral and cerebellar white matter, and there are perivascular macrophages containing lipofuscin-like pigments and spheroid bodies in the neuropili of several brainstem nuclei. Babies with the condition may be born preterm with ichthyosis, which is generalized brownish-yellow in colour and associated with a severe pruritus. Developmental delay and spasticity are apparent by the first or second year, leading to contractures in the lower ex- tremities and wheelchair dependency in adolescence. Cognition is impaired in most patients. Pseudobulbar dysarthria, delayed speech, and seizures are common. Ophthalmological abnormalities include photophobia, macular dystrophy, and decreased visual acuity. After several years, glistening white dots surround the macular region of the retina, form of crystalline maculopathy. EEG shows sym- metrical slow background activity with no epileptiform pattern. Cerebral MRI studies reveal multifocal areas of delayed myelin- ation, hyperintense signal abnormality in the periventricular zone, and mild ventricular enlargement in the oldest patients. On MRS of the cerebral white matter and basal ganglia, there is a distinct diag- nostic sharp lipid peak, believed to arise from the accumulation of long-chain fatty alcohols or aldehydes. Treatment has been attempted with a low-fat diet supplemented with medium-chain fatty acids but was not successful. Beneficial effects have been described using the LTB4 synthesis inhibitor Zileuton. The accumulation of leukotrienes due to FALDH- dependent deficient degradation is presumed to play an important part in the inflammatory reactions seen in the skin of SLS patients. The hypolipidaemic drug, bezafibrate, has been shown to induce residual FALDH activity in patient

fibroblasts and may be a thera- peutic option. Cerebrotendinous xanthomatosis This rare but underdiagnosed disorder should always be con- sidered in the differential diagnosis of a leucodystrophy, because it is a treatable condition. Among Moroccan Jews the incidence of cerebrotendinous xanthomatosis (CTX) is 1 in 108 and in the gen- eral US population its prevalence is estimated to be 3 to 5 in 100 000. The 5α-dihydro-derivative of cholesterol, cholestanol, is increased 10- to100-fold in CTX. It is present in the diet but its accumula- tion in the nervous system apparently results from increased en- dogenous production and impairment to its egress as a result of the blood–brain barrier. Mutations in the sterol 27-hydroxylase gene (CYP27) cause a block in bile acid synthesis, leading to absence of chenodeoxycholic acid in the bile and excretion of bile alcohols (bile acid precursors) in the bile and urine. Absence of chenodeoxycholic acid leads to upregulation of endogenous bile acid synthesis. Brain atrophy with multiple yellowish deposits in the plexus choroideus and in brain white matter are evident on autopsy. Microscopically, multiple dispersed lipid crystal clefts and granu- lomatous lesions in the cerebellar hemispheres, demyelination and perivascular accumulation of foamy macrophages in the globus pallidus, and extracellular deposition of homogeneous myelin- like material in periventricular areas are evident. Examination of spinal cord may show demyelination, gliosis, and involvement of the long tracts. Nerve biopsy reveals primary axonal degeneration,

section 24 Neurological disorders 6222 demyelination, and remyelination. Xanthomas are an accumulation of xanthoma cells and multiple, dispersed lipid crystal clefts. Symptoms commonly appear in childhood or during the second decade, but patients may present in the neonatal period or in middle age. Patients with CTX have an average age of 35 years at the time of diagnosis and a diagnostic delay of 16 years. There may be difficulty in school due to slowly progressive intellectual impairment, behav- ioural difficulties, and psychiatric symptoms. Neurological findings almost invariably develop and include cerebellar and pyramidal tract signs, peripheral neuropathy, and seizures. The neurological manifestations may be classified into two main clinical subgroups, the classic form (cerebellar and supratentorial symptoms) and the spinal form (chronic myelopathy). Other manifestations include cataracts, tendon and tuberous xanthomas (especially of the Achilles tendon), diarrhoea, osteo- porosis, and bone fractures. Within the neonatal period, prolonged cholestatic jaundice may be observed. Eye signs in addition to cata- racts include optic disc pallor, premature retinal senescence, palpe- bral xanthelasmas, corneal lipoid arcus, and proptosis. Premature atherosclerosis and cardiovascular disease have been reported among the multiple clinical manifestations of CTX. The biochemical abnormalities in CTX include a plasma cholestanol concentration 5- to 10-fold greater than normal (330 ± 30 μg/dl), a urine bile alcohol concentration of 14 000 ± 3500 nmol/litre, and a plasma bile alcohol concentration more than 500- to 1000-fold greater than normal (8.48 ± 3.67 nmol/litre). Imaging studies dis- close cerebellar and spinal cord atrophy, symmetric hyperintensities in the dentate nuclei and brain white matter hypodensity. The cere- bellar white matter is especially involved and there is hypersensitivity of the dentate nuclei bilaterally on the FLAIR sequence. A mainly spinal cord syndrome can occur with white matter abnormalities in the lateral and dorsal columns of the spinal cord. Long-term oral therapy with chenodeoxycholic acid (750 mg/ day), most effective in presymptomatic individuals, has been shown to suppress the abnormal bile acid synthesis, correct the biochemical abnormalities, and reverse the progression of CTX. Although HMG- CoA (hydroxymethylglutaryl coenzyme A) reductase inhibitors re- duce serum cholesterol levels, caution is exercised because they can exacerbate the mitochondrial impairment. Although cholic acid can normalize plasma cholestanol and improve nonneurological symp- toms, only CDCA can improve the neurological symptoms in

pa- tients with CTX. Long-term replacement therapy with CDCA can increase bone mineral content. Combination therapy with CDCA (300 mg/d) and pravastatin (10 mg/d) can improve lipoprotein metabolism, inhibit cholesterol synthesis, and reduce plasma levels of cholestanol and plant sterols. Lysosomal diseases Lysosomal storage disorders (LSDs) are a heterogeneous group of conditions mostly related to failure of degradation of one or more macromolecules which results in their accumulation within tis- sues (Table 24.17.2). Together these disorders, numbering over 50, have an incidence of 1 in 5000 to 7000 births. Two thirds of these conditions are enzyme deficiencies wherein the un-metabolized or partially metabolized substrate accumulates. The stored materials are by products of the cellular turnover of complex glycoproteins, glycolipids, glycosaminoglycans (mucopolysaccharides), and oligosaccharides. Whereas lysosomal enzymes are ubiquitously expressed, the sub- strate on which they act may be confined to a single organ or system, as in Krabbe disease, or distributed more widely causing multi- systemic manifestations, as in Gaucher disease. Signs of disease manifestations may become evident prenatally, at birth, or at any time from infancy to adulthood. Here LSDs that involve the central and/or peripheral nervous system are considered. Clinical genetics Most LSDs are inherited in an autosomal recessive manner, some are X-linked. The LSDs that affect the nervous system are neurodegenerative in nature with onset of clinical neurological symptoms usually following some period of normal development. This characteristic feature allows recognition of a storage disease on clinical evaluation. The age of onset and course of the disease is often dictated by the residual enzyme activity which in turn depends on the severity of the mutation. Homozygous or compound heterozy- gous null and/or severe deleterious mutations often lead to absent or almost absent residual enzyme along with the classic infantile or late-infantile presentation and a rapidly progressive and often fatal disease course. Most LSDs were originally described in this classic form and bear the name of the physician(s) who identified them. However, homozygous or compound heterozygous milder missense mutations usually allow some residual enzyme activity. Very often, this leads to later-onset and relatively slowly progres- sive disease. In addition, there is a remarkable change in phenotypic expression such that often the organ involvement or the clinical feature that is considered hallmark of the infantile presentation is no longer evident. A striking example of this may be late-onset Tay–Sachs disease, which does not present with cherry red spot, seizures, cognitive decline, or macrocephaly. Instead it is a anterior horn cell and cerebellar disease with variable psychiatric features. Or late-onset forms of Pompe disease where there is no significant cardiac involvement. This unexpected and unanticipated change in phenotype as well as the likelihood that the late-onset forms mimic other common dis- orders (e.g. limb-girdle muscular dystrophy and late-onset Pompe disease, leads to under significant delayed diagnosis and misdiagnosis). The diagnostic delay in late-onset forms of LSDs is consid- erable mostly related to lack of awareness among physicians about the wide spectrum of phenotypic expression and true prevalence of LSDs. This is compounded by the perception that since most of these disorders do not have definitive therapies, lack of accurate diagnosis may not change medical management in an individual pa- tient. However, newer therapies are rapidly being developed. Also, accurate diagnosis permits appropriate genetic counselling for the patient and family and allows apt prognostication. Among Ashkenazi Jews, the frequency of the carrier state for cer- tain of the lysosomal storage diseases (LSDs) is higher than in the general population. For this reason, screening couples before con- ception or in the early stages of a pregnancy is done to determine their carrier status for these disorders, which include Tay–Sachs dis- ease, Niemann–Pick disease types A and B, and mucolipidosis IV. In each pregnancy of a couple in which both partners are carriers of the same recessive trait, there is a 25% risk of an affected fetus. Monitoring of their

pregnancies by amniocentesis or chronic villous

24.17 Inherited neurodegenerative diseases 6223 Table 24.17.2 Lysosomal storage diseases Stored substrate Disease Enzyme/protein deficiency Gene locus Sphingolipids GM2 gangliosides, glycolipids, globoside oligosaccharides Tay–Sachs disease α Subunit of β-hexoaminidase 15q23–24 GM2 gangliosides (three types) Sandhoff's disease β Subunit of β-hexoaminidase 5q13 GM2 gangliosides GM2 activator 5q32–33 GM2 gangliosides, AB variant GM1 gangliosides, oligosaccharides, keratin sulphate, glycolipids GM1 gangliosides (three types) β-Galactosidase 3p21-3pter Sulphatides Metachromatic leucodystrophy Arylsulphatase A (galactose-3-sulphatase) 22q13.31-qter GM1 gangliosides, sphingomyelin, glycolipids, sulphatide Metachromatic leucodystrophy variant Saposin B activator 10q21 Galactosylceramides Krabbe's disease Galactocerebrosidase 14q31 α-Galactosylsphingolipids, oligosaccharides Fabry's disease α-Galactosidase A Xq22 Glucosylceramide, globosides Gaucher's disease (three types)a β-Glucosidase 1q21 Glucosylceramide, globosides Gaucher's disease (variant) Saposin C 10q21 Ceramide Farber's disease (seven types) Acid ceramidase 8p22–21.2 Sphingomyelin Niemann–Pick disease types A and B Sphingomyelinase 11p15.1–15.4 Mucopolysaccharides (glycosaminoglycans) Dermatan sulphate and heparin sulphate MPS I, Hurler–Scheie α-l-Iduronidase 4p16.3 Heparan sulphate MPS IIIA, Sanfilippo A Sulphamidase 17q25.3 MPS IIIB, Sanfilippo B α-N-Acetylglucosaminidase 17q21.1 MPS IIIC, Sanfilippo C Acetyl-CoA:α-glucosaminide-N-acetyltransferase MPS IIID, Sanfilippo D N-acetylglucosamine-6-sulphatase 12q14 Keratan sulphate MPS IVA, Morquio A Galactosamine-6-sulphatase 16q24.3 MPS IVB, Morquio B β-d-Galactosidase 3p21.33 Dermatan sulphate MPS VI, Maroteaux–Lamy N-Acetylgalactosamine-4-sulphatase 5q13–14 Dermatan sulphate and heparan sulphate MPS VII, sly Hyaluronidase 7q21.1–22 Hyaluronan MPS IX β-d-Glucuronidase 3p21.3 Glycogen Glycogen Pompe's disease, glycogen storage disease type IIA α-d-Glucosidase 17q25 Glycogen Danon's disease Lysosomal associated membrane protein-2 (LAMP-2) Xq24 Oligosaccharides/glycopeptides α-Mannoside α-Mannosidosis α-Mannosidase 19p13.2–q12 β-Mannoside β-Mannosidosis β-Mannosidase 4q22-25 α-Fucosides, glycolipids α-Fucosidosis α-Fucosidase 1p34.1–36.1 α-N-Acetylgalactosaminide Schindler–Kanzaki disease α-N-Acetylgalactosaminidase 22q13.1–13 Sialyloligosaccharides Sialidosis α-Neuraminidase 6p21.3 Aspartylglucosamine Aspartylglucosaminuria Aspartylglucosaminidase 4q34-35 Multiple enzyme deficiencies Glycolipids, oligosaccharides Mucolipidosis II (I-cell disease); mucolipidosis III (pseudo-Hurler's polydystrophy)—three complementation groups) N-Acetylglucosamine-1-phosphotransferase 4q21–q23 Mucolipidosis III subtype C γ subunit mutations on 16p Galactosialidosis Protective protein/cathepsin A 20 (continued)

section 24 Neurological disorders 6224 biopsy permits interruption at an early stage. The birth incidence of several of these disorders has decreased in this ethnic community due to couple screening and counselling. Another type of preven- tion programme, popular among the Orthodox Jewish population, involves nonstigmatizing premarital testing permitting marriages to be arranged that avoid the possibility of two carriers for the same disease trait marrying. Families, with affected previous child, can access prenatal testing of the subsequent conceptus using either information on the mu- tations present in the family or through testing of enzyme activity in the chorionic villous cells or the cultured amniotic fluid cells. Newborn screening is also being developed for those LSDs in which an intervention, such as umbilical cord stem cell transplantation (e.g. Krabbe disease) or enzyme replacement therapy (e.g. Pompe disease), may be done in the early newborn period to prevent dis- ease progression. The application of multiplex systems that measure the

activities of several lysosomal enzymes simultaneously either by immunofluorescent probing or by tandem mass spectroscopy, with novel substrates, are exciting new developments that make neonatal screening possible. In all cases in which a diagnosis of an LSD is made, family members should be offered genetic counselling and should be encouraged to inform relatives of their increased risk of carrying the trait for the disease. Sphingolipidoses The sphingolipidoses are characterized by abnormalities in the me- tabolism of various glycolipid substrates that are present within membranes of nerve cells and myelin. Most of these disorders are neurodegenerative in nature. Glycosphingolipids (GSLs) undergo degradation within lysosomes through the sequential action of spe- cific acid hydrolases with the assistance of nonenzymatic glycopro- tein cofactors, so-called sphingolipid activator proteins (or saposins [SAPs]). Ultrastructural studies of tissues from patients with GSL storage diseases typically reveal the presence of characteristic inclu- sions such as the membranous cytoplasmic bodies present in pa- tients with GM1 and GM2 gangliosidoses. Gangliosidoses The carbohydrate moieties of the glycocalyx (‘sweet husk’) that sur- rounds cells are involved in diverse functions such as (i) cell differ- entiation, (ii) cell–cell interactions, and (iii) signal transduction. Cells in the CNS express an abundance of cell surface glycosylated proteins and lipids. Lipid rafts, which are sites of signal transduction, are enriched in glycosphingolipids (GSLs). A group of sialylated phosphorus-free GSLs, known as gangliosides, are essential for normal neural development and function. The gangliosides com- prise of a ceramide backbone, to which glycans are attached through a single glycosidic linkage at the 1-hydroxyl position. The glycan chains contain one to four (and unusually up to 7) sialic residues. Svennerholm, based on the placement of their sialic acid residues and their distinct chromatographic mobility, assigned the nomen- clature of these ganglioside substrates. Thus G denotes ganglioside, M/D/T/Q (mono-/di-/tri-/tetra-, and so on) indicate the number of sialic acid residues, with an assigned number being originally based on the migration order of the gangliosides on thin layer chromatog- raphy (e.g. GM3 > GM2 > GM1). Catabolism of the carbohydrate portion of gangliosides occurs in the lysosomes where removal of glycosyl residues is catalysed by specific glycosidases. While present in most tissues including peripheral neurons, gan- gliosides are found in greatest concentration in the grey matter of the brain. Disorders of ganglioside metabolism are classified according to the specific enzyme deficiency and the resultant accumulation of its substrates. Each disorder is further categorized by age of onset into classic (early or late) infantile or later-onset (juvenile or adult) forms. Age of onset and degree of disease expression are influenced, in part, by the degree of residual enzyme activity. Secondary gan- glioside accumulation occurs in other LSDs such as the MPSs and Niemann–Pick disease type C. GM1 gangliosidosis GM1 gangliosidosis is an autosomal recessive LSD caused by defi- ciency of the enzyme β-galactosidase (β-Gal, GLB1) with estimated incidence of 1:100 000–200 000 live births. The GLB1 protein is Stored substrate Disease Enzyme/protein deficiency Gene locus Sulphatides, glycolipids, glycosaminoglycans Multiple sulphatases SUMF-1 3p26 Lipids Cholesterol esters Wolman’s disease, cholesteryl ester storage disease Acid lipase 10q23.2–q23.3 Cholesterol, sphingomyelin Niemann–Pick disease type C NPC1; HE1 18q11–12; 14124.3 Monosaccharides/amino acid monomers Sialic acid, glucuronic acid Salla’s disease, infantile free sialic acid
storage disease Sialin 6q14–15 Cystine Cystinosis Cystinosis 17p13 Peptides Bone proteins Pyknodysostosis Cathepsin K 1q21 S-Acylated proteins Palmitoylated proteins Infantile neuronal ceroid lipofuscinosis Palmitoyl-protein thioesterase 1p32 Pepstatin-insensitive lyosomal peptidase Late-infantile neuronal ceroid lipofuscinosis Pepstatin-insensitive lysosomal peptidase 11p15
Table 24.17.2 Continued

24.17 Inherited neurodegenerative diseases 6225 encoded by the GLB1 gene (MIM 230500), mapped on the 3p21.33 chromosome. To date more than 130 mutations have been described. It is associated with the neuronal storage of the monosialoganglioside GM1. Normally 20% of all gangliosides found in the brain and 80% of gangliosides in myelin are the monosialoganglioside GM1. Several other substrates of β-galactosidase, including lactosylceramide, asialofetuin, oligosaccharides carrying terminal β-linked galactose and keratan sulphate, also accumulate and this may explain the pres- ence of dysmorphic facial features reminiscent of the MPS disorders in the early infantile form of GM1 gangliosidosis. Morquio B syn- drome is an alleilic disorders where GLB1 is defective with respect to keratan sulphate. Primary neurological involvement is not known in Morquio B syndrome. Histological examination of the brain in infantile GM1 gangliosidosis shows neurons and glial cells with distended cytoplasm and eccen- trically placed pyknotic nuclei. The nerve cell bodies of the neurons are ballooned. Foam cells with highly vacuolated cytoplasm was noted in visceral organs including liver, spleen, bone marrow, lung, adrenal medulla, and thyroid. Electron microscopy shows concen- trically arranged inclusion bodies, which largely replace normal cytoplasmic constituents. In later-onset forms marked GM1 ganglio- side storage is seen in the basal ganglia. Three main clinical forms have been identified: type I (infantile), type II (late-infantile/juvenile), and type III (adult) with overlapping manifestations. Early infantile GM1 gangliosidosis presents with hypotonia, feeding difficulties, and failure to thrive in the first weeks to 6 months of life. A macular cherry red spot is found in about 50% of cases, and there is a startle response similar to that seen in Tay– Sachs disease. Cherry red spot represents the normal ganglion cell- free region of fovea which appears bright red against the abnormally pale retina, where lipid-laden ganglion cells produce a white ring or halo. Dysmorphic facial features such as frontal bossing, wide depressed nasal bridge, gingival hypertrophy, or thickened alveolar ridges are prominent. Hepatosplenomegaly as well as bone deform- ities referred to as dysostosis multiplex, similar to those found in the MPS disorders, including hypoplasia and anterior beaking of the thoracolumbar vertebrae and widening of the diaphysis of long bone, are also noted. Cardiac complications include enlargement of the heart with thickening of the heart valves and endocardial fibroelastosis, leading to valvular incompetence and cardiac failure. Hydrops fetalis may be the presenting feature at birth in 6% of cases. The course is relentlessly progressive leading to spasticity, tonic spasms, and pyramidal signs with decerebrate rigidity by the second year with or without seizures. Respiratory failure and bronchopneu- monia lead to death, usually by 2 years. The late-infantile form has an onset usually between 7 and 36 months, often with walking difficulty and frequent falls. Facial dysmorphism, skeletal deformities, and organomegaly are less prominent. Progression of the disease leads to seizures, spastic quadriparesis, and pseudobulbar signs such as drooling and dys- phagia. Death occurs between the ages of 3 and 10 years. The late-onset form, with onset beyond three years of age, is a protracted illness with dysarthria, dystonia, and mild-to-moderate intellectual impairment, usually developing in late childhood or adolescence, but signs and symptoms may be delayed until the third or fourth decade of life. There is vacuolation of periph- eral blood lymphocytes, and the presence of galactose-containing oligosaccharides and keratan sulphate in urine, findings that help to distinguish GM1 gangliosidosis from mucolipidosis II (I-cell dis- ease), because both can present with dysmorphic facial features and hepatosplenomegaly. Diagnosis is established by assay of β-Gal activity in peripheral blood leucocytes and cultured skin fibroblasts, or prenatally using cultured chorionic villous sample (CVS) or amniocytes. Only symp- tomatic treatment is available. In animal studies, oral administra- tion of bicyclic 1-deoxygalactonojirimycin derivative (6S-NBI-DGJ) ameliorated the brain pathology of GM1 gangliosidosis mouse model. Systemic AAV9 gene transfer in adult mice with GM1 gangliosidosis

reduces lysosomal storage in CNS and extends lifespan. GM2 gangliosidoses The GM2 gangliosidoses are a group of heterogeneous clinical variants associated with the neuronal storage of the monosialoganglioside GM2, caused by mutations in genes encoding α or β subunit of hexosaminidase A (Hex-A) or the GM2 activator protein. The three major forms of GM2 gangliosidoses are (1) Tay–Sachs disease, caused by mutations of HEXA that result in a deficiency of HEXA but normal HEXB activity (2) Sandhoff disease, caused by mutations of HEXB that result in a deficiency of both isoenzymes HEXA and HEXB and (3) the AB variant, caused by mutations in GM2A that lead to an inability to form a functional ganglioside GM2/GM2A complex. The Hex-A enzyme, with molecular mass of approximately 100 kDa, is a trimer consisting of one α- and two β-subunits, encoded by genes situated on different chromosomes. Mutations in the β-subunit lead to deficiency of Hex-B as well, which is a tetrameric homopolymer of β subunits. The B1 variant of GM2 gangliosidosis, which has a high incidence in Portugal, results from altered substrate specificity of Hex-A. In this variant the mutated enzyme retains the ability to de- grade the artificial substrate used in diagnostic assays, but not the natural substrate in vivo or the sulphated artificial substrate. Ultrastructural examination in GM2 gangliosidosis reveals neur- onal GM2 ganglioside storage throughout the cortex and the deep grey nuclei, the spinal cord, and the autonomic ganglia. Characteristic pathological features are axonal hillock enlargement, known as meganeurite formation, and sprouting of new synapse-covered den- dritic neurites at the axon hillock termed ‘ectopic dendritogenesis’, as well as axonal spheroid formation or neuroaxonal dystrophy. Spheroids are focal enlargements of various sizes distributed along myelinated and unmyelinated axons in the grey and white matter, consisting of multivesicular and dense bodies, mitochondria, and other organelles. This suggests that there is defective endocytic trafficking within axons. The incidence in the general population has been estimated at 1 in 112 000 live births, although the disease was highly prevalent among Ashkenazi Jews (1 in 3900 live births). Successful implementation of carrier screening programmes for at- risk couples has remedied this situation. The ‘classic’ infantile form of Tay–Sachs disease (TSD) is named after a British ophthalmologist, Warren Tay, and an American neur- ologist, Bernard Sachs. It presents in infancy with psychomotor de- terioration, poor head control, easy startle, axial hypotonia, bilateral pyramidal signs, and cortical blindness (pupillary responses are pre- served). A characteristic hallmark of the disease is the presence of a macular cherry red spot. In the second year of life, brain enlarge- ment (not hydrocephalus) leads to progressive megalencephaly; however, with further loss of the neurons and gliosis, the ventricles dilate. Progressive neurological deterioration leads to a spastic state

 and cachexia. Generalized tonic-clonic and simple motor seizures that occur in later stages necessitate multiple anticonvulsant medi- cations and are often the focus of clinical care. Death usually occurs between 3 and 5 years of age. The AB variant, caused by deficiency of the GM2 activator, has a phenotype that is indistinguishable from the infantile form; however may present somewhat later than the classic infantile form. This diagnosis is suspected when the labora- tory test results for assays of Hex-A and -B enzyme activity using artificial substrates are normal and the clinical presentation suggests gangliosidoses. The later-onset forms of GM2 gangliosidosis follow a protracted course and there is no ethnic predilection. Differences in the age of onset and disease progression, presumably determined by the severity of the underlying mutation, distinguish the childhood form, which has an onset between ages 3 and 6 years (chronic GM2 gangliosidosis) from the adult-onset variant or late-onset TSD (LOTS), appearing in the teens or early adulthood. The pheno- type of the B1 variant is similar to that of the childhood-onset form. Affected children develop dysarthria and gait difficulty, due to spastic

paraparesis, which may be accompanied by tonic-clonic or myoclonic seizures. Cerebellar atrophy is common. Psychiatric disturbances and neuropathy is more prevalent in patients with the Sandhoff variant than in those with the Tay–Sachs variant. Disease progression is marked by spasticity, rigidity, and dementia, ending in a vegetative state leading to death by the age of 15 years. LOTS primarily presents as a very slowly progressive disorder with anterior horn cell and cerebellar degeneration. Proximal muscle weakness, ataxia with cerebellar atrophy, and fasciculations are prominent in the later-onset forms, often leading to a wheelchair-dependent state over several years of disease duration. Age of onset is variable from teens to the fourties. Psychiatric dis- turbances, including frank psychosis, may be the initial manifest- ation of disease, particularly among younger patients. Vision and optic fundi are normal, although some cognitive decline is frequently encountered. The adult-onset phenotype this carries none of signature characteristics of infantile Tay–Sachs disease namely cognitive decline, visual failure with cherry red spot, seizures, or macrocephaly. Therefore, it has a significantly high risk of delayed or missed diagnosis. Late-onset GM2 gangliosidosis should be con- sidered in the differential diagnosis of adult patients with signs of lower motor neuron and cerebellar dysfunction. Some adult-onset patients may live into their 50s or 60s. Sandhoff's disease (SD), a pan-ethnic disorder, is caused by mutations in the β-subunit of Hex-A and -B. Although the age of onset and clinical course are similar to TSD, organomegaly, N- acetylglucosamine-containing oligosaccharides in urine, and oc- casional cardiomyopathy are distinguishing features. Dysesthetic peripheral neuropathy may predominate in late-onset forms of Sandoff along with anterior horn cell and cerebellar features. The diagnosis is ascertained by assays of total hexosaminidase and Hex-A activity in leucocytes, and cultured skin fibroblasts comple- mented by analysis of the underlying Hex-A gene mutations. Prenatal diagnosis of the GM2 gangliosidoses is available. Biochemical and/or molecular tests are preformed on cultured cells obtained by CVS or amniocentesis. There is no definitive therapy for GM2 gangliosidoses. Substrate reduction therapy, based on the inhibition of glucosylceramide synthesis using the iminosugar miglustat, was not beneficial in ameliorating the disease course in LOTS. There have been prelim- inary studies involving pyrimethamine as a chaperone to HexA enzyme enhancement for LOTS; further studies are necessary to determine the efficacy. Gene therapy is under intense investigation. Jacob sheep, a naturally occurring animal model of Tay–Sachs disease offers promise as a means for trials of gene therapy. Fabry disease (see Chapter 12.8) Fabry Disease (FD, OMIM 301500) or Angiokeratoma corporis diffusum was originally described by Anderson and Fabry in 1898. FD is a slowly progressive X-linked lysosomal disorder characterized by storage of glycolipids consisting mainly of globotriasoylceramide, as a result of a-galactosidase A deficiency. The storage occurs mainly in the myocardial muscle cells, glomerular and tubular epi- thelia of the kidney, and vascular smooth muscle cells and endo- thelia leading to progressive organ failure. The reported incidence ranges from 1:40 000 to 1:117 000 worldwide. The disease is caused by mainly missense and nonsense mutations, but also small and large deletions. There is significant inter and intrafamilial variability. However, mutations leading to a complete loss of function are asso- ciated with the 'classical disease phenotype', with childhood onset in boys. Conversely, residual enzyme activity might lead to slow pro- gression of the disease leading to the cardiac or renal variants with delayed onset. The primary cause of morbidity and mortality in FD is kidney and heart involvement. Prior to dialysis and ERT, average age of death in men with FD was 41 years. Neurological manifestations of FD are discussed here. Although storage of lipid is described in certain nuclei such as the amygdaloid body, subiculum, and dorsal vagus nucleus of the medulla oblongata FD is not considered to be a neurodegenerative disease. The central nervous system manifest- ations are primarily related to small and large vessel disease. There are

several distinct and unusual symptoms associated with the classic phenotype of FD which is seen in young boys starting in the pre-teen to adolescent years, usually between 6–8 years. The most striking feature of classic FD is neuropathic pain in the distal extremities with Fabry crisis presenting as acute episodic pain typ- ically beginning in hands and feet and may radiate proximally, often precipitated by stress, heat, exercise, or fever. Patients also suffer a chronic burning or tingling pain in extremities, acroparesthesias. Pain is one of the most disabling symptom in FD. In addition to painful neuropathy, patients sometimes have arthralgias of un- known origin. Dysautonomic features due to involvement of the autonomic nervous system especially the A ∂ fibres such as hypo or anhidrosis, reduced salivation, and lachrymation, gastrointes- tinal dysmotility, cardiac dysrhythmia, and reduced cutaneous flare after histamine injections are common manifestations of FD. Gastrointestinal symptoms in the form of abdominal discomfort, nausea, vomiting, and diarrhoea occur. Angiokeratomas develop in virtually all patients in childhood or adolescence characteristically described below the umbilicus in the genital areas, buttocks, and thighs along with palms of hands, which increase in number and distribution over years. The most common eye finding in patients with FD is cornea verticillata. Despite a myriad of pathognomonic clinical findings FD is significantly underdiagnosed especially in young boys and men. Neurological examination usually reveals loss of temperature sen- sation in hands and feet and a reduced tolerance to low temperature

24.17 Inherited neurodegenerative diseases 6227 exposure. Nerve conduction studies, which assess only large myelin- ated fibres, are generally normal. Sophisticated techniques to assess the small fibre involvement such as quantitative sensory test (QST), a biophysical method based on computerized automated sensory testing to measure detection thresholds for warm and cold in the feet and hands, revealed significantly elevated detection thresholds for warm and cold stimuli in the foot and for cold in the hands of FD patients compared to controls. Intraepidermal nerve fibre density (IENFD) is positively correlated in males with Glomerular filtration rate (GFR). The classic phenotype of FD is rarely seen in heterozygous women, however many of the carriers have isolated or multiple manifestations of the disease. The process of lyonization, random X-chromosomal inactivation during embryogenesis, results in varying proportion of cells carrying the normal or the abnormal X- chromosome with the α-gal mutation. Apart from the episodic and chronic pain, cerebrovascular dis- ease remains the major cause of morbidity and early mortality in patients with FD. Various factors have been implicated in the patho- genesis of cerebrovascular disease in FD. Intracranial small arteries and arterioles show accumulation of Gb-3 within endothelial cells causing narrowing and may lead to ischaemia. There is evidence for endothelial dysfunction as well as a procoagulant state with in- creased platelet aggregation. There have been numerous studies demonstrating ectasia and dilatation of large vessels especially in the posterior circulation, stenosis and thickening of small vessels, and altered cerebral blood flow. There is increased risk of ischaemic small and large vessel strokes in men and women with FD with up to 25 % of the patients suffering cerebrovascular events over their life course. Chronic occlusive small vessel disease leads to leukoaraiosis whereas cardioembolic phenomenon contributes to territorial is- chaemic strokes. Studies show the mean age of stroke in men and women to be 39 and 46 respectively; thus FD represents an im- portant cause of cryptogenic stroke. Hyperintensities of the thalamic posterior region or the pulvinar sign on MRI T1-weighted images are noted by the third decade in about one fourth of patients and frequency increased with age. Corresponding images on CT scan show increased density likely due to calcification. Arterial spin tagging (AST) MRI images and positron emission tomographic (PET) studies reveal increased cerebral blood flow in the

posterior circulation suggesting that hyperperfusion may have induced dystrophic posterior thalamic cal- cification, with a selective vulnerability of the putamen. Impairment of the vasoreactivity and autoregulation in the posterior circulation, probably due to pericytes, endothelial cells, or nitric oxide pathway dysfunction result in hyperperfusion followed by increasing capil- lary leakage. An increased basilar diameter has been shown to rep- resent another radiological finding suggestive of FD. Patients with FD require intensive pain management. Pain is often refractyory to several medications as well as other modalities of treatment. Patients are often prescribed antiplatelet therapy for prevention of cardiac and cerebrovascular disease. ERT for FD was approved in 2001 in Europe and 2003 in the United States. Success with ERT has been limited. ERT in more advanced stages of FD does not halt disease progression especially in patients with decreased renal function. Males with less advanced disease (e.g. relatively pre- served renal function or absence of LVH at start of therapy), also demonstrate disease progression despite ERT. However, in males with a GFR less than 60 ml/min/1.73 m2 treated with ERT, decline of renal function is less pronounced when compared to the untreated group. ERT did have a beneficial effect on the course of LV mass when compared to untreated groups. It is known that new WMLs develop despite ERT. In 2015, chaperone therapy, migalastat, was ap- proved for FD in Europe. No data on efficacy of chaperone therapy for CNS involvement in FD are available. Gaucher disease Gaucher disease, the most common lysosomal storage dis- order with an estimated frequency of about 1 in 50 000, is caused by the deficiency of the lysosomal enzyme glucocerebrosidase (acid β-glucosidase), leading to the accumulation of its substrate, glucocerebroside (glucosylceramide) within cells of monocyte/ macrophage lineage. The three major clinical subtypes are delin- eated based on the presence or absence of neurological involvement as well as the age of onset, rapidity of disease progression, and the rate and severity of neurological deterioration, when present. In contrast to the large amount of lipid stored in the liver and spleen, there is no significant accumulation of glucocerebroside in the brain. Severe glucocerebrosidase deficiency leads to produc- tion of glucosylsphingosine (psychosine), an alternative neurotoxic metabolic by product, which could play a contributory role in the pri- mary neurological involvement seen in certain subtypes of Gaucher disease. Neuropathological studies reveal lipid-filled cells in the perivascular Virchow–Robin spaces and neuronophagic microglial nodules in several regions of the brain (e.g. cortex, thalamus, basal ganglia, brainstem, and cerebellum) and in the spinal cord. Type I Gaucher disease, a pan-ethnic disorder with high preva- lence among the Ashkenazi Jewish population (carrier frequency about 1 in 20), usually refers to the nonneuropathic disease asso- ciated with hepatosplenomegaly, anaemia, thrombocytopenia, and pulmonary involvement. There are six to eight common mutations described of which N370S is the commonest mutation. Having at least one allele with this mutation confers significantly decreased or no possibility of neuronopathic disease. There is a wide spectrum of age of onset and severity of disease ranging from early onset sever disease to late adult forms with minimal hepatosplenomegaly even within individuals who are hiomozygous for N370S mutations. Being affected with type I Gaucher disease or even being a carrier in- creases the risk of developing Parkinson’s disease by about five fold. The onset of Parkinson’s disease is consistently earlier in these pa- tients with higher cognitive involvement, although there is no other phenotypic or pathological distinction from idiopathic Parkinson’s disease noted. In type II Gaucher disease, disease onset is before 12 months of age. In this acute neuropathic form, infants develop spasticity with head retraction (opisthotonus), dysphagia, and a rapidly fatal course; death usually occurs between 2 and 3 years of age. Laryngeal stridor, trismus, seizures, and aspiration pneumonia are frequent complications. Type III Gaucher disease, found in about 5% of patients with Gaucher disease, is a chronic disorder with variable age of onset, usually

before the age of 10 years. Neurological features include gaze initiation failure, tonic-clonic and myoclonic seizures ataxia, and extrapyramidal rigidity. Severe pulmonary involvement is often present. The Norbottnian variant of type III Gaucher disease presents with neurological problems which may be restricted to supranuclear

section 24 Neurological disorders 6228 horizontal gaze palsy despite the presence of significant extra- neurological systemic problems. ERT is now the mainstay of treatment for Gaucher disease, al- though it does not alter the course of neurological deterioration in patients with type II or type III Gaucher disease. Substrate reduc- tion therapy (SRT) with both miglustat and eliglustat tartrate has been shown to be effective in ameliorating several clinical features of Gaucher disease and was approved for use in type I Gaucher pa- tients, although role of substrate reduction therapy in neuropathic Gaucher disease still has to be elucidated. Niemann–Pick disease Niemann–Pick disease (NPD) represents a group of auto- somal recessive disorders associated with mutations of the acid sphingomyelinase (ASM) gene, resulting in primary deficiency of sphingomyelinase causing progressive storage of sphingomyelin (phosphorylcholine) in the reticuloendothelial system. NPD sub- types A (infantile neuropathic) and B (later-onset nonneuropathic) represent the spectrum of allelic variants. NPD subtypes C and D are also allelic disorders due to mutations of either the NPC1 or the NPC2 gene, which may be associated with mild secondary ASM de- ficiency. Mutations in NPC1 or -2 leads to disruption in the traf- ficking and/or metabolism of cholesterol and sphingolipid. Early infantile neuronopathic NPD type A presents within the first few weeks or months with failure to thrive and hepatomegaly; over time the liver and spleen become massive. This is followed by neurological regression and the appearance of the macular cherry red spot; psychomotor development progresses no further than the 12-month level, after which neurologic deterioration is relentless. Interstitial lung disease caused by storage of sphingomyelin in pul- monary macrophages results in frequent respiratory infections and often respiratory failure. This ultimately leads to liver failure with ascites and jaundice, cachexia, rigidity, and opisthotonus. Death occurs in the second or third year of life. NPD type B is later in onset and milder in manifestations than NPD type A, character- ized by hepatosplenomegaly with progressive hypersplenism and stable liver dysfunction, gradual deterioration in pulmonary func- tion, osteopenia, and atherogenic lipid profile. Progressive and/or clinically significant neurologic manifestations occur infrequently. Survival to adulthood can occur. There are vacuoles within periph- eral lymphocytes and monocytes, as well as foam cells in the bone marrow. Deficient ASM activity in leucocytes or cultured skin fibro- blasts confirms the diagnosis of NPD types A and B. NPD type C has an estimated incidence of 1 in 150 000. Mutations in the gene NPC1, which encodes a large transmembrane glyco- protein localized primarily in the late endosomes, causes approxi- mately 95% of cases, whereas a smaller group of patients has been shown to have a defect of the NPC2 gene, which encodes a small soluble lysosomal protein with cholesterol-binding properties. It is a neurovisceral lipid storage disorder neuropathologically charac- terized by axonal spheroids, intraneuronal cytoplasmic inclusions, and neuronal loss. About 50 to 60% of cases are considered to have the classic pres- entation with a benign, self-limiting jaundice in early infancy, followed by normal initial development. Between the ages of 3 and 8 years these children develop hepatosplenomegaly, clumsi- ness, ataxia, and supranuclear vertical gaze palsy, accompanied by blinking or head thrusting, eventually progressing to dysarthria, dysphagia, and cognitive decline. Characteristic neurological manifestations include saccadic eye movement abnormalities or vertical supranuclear gaze palsy, cerebellar signs, and gelastic cataplexy. Seizures and dystonia are also common. Neurological deterioration is relentless leading to a bed bound state and even- tually

death by late second or third decade. Late-onset forms are increasingly recognized with typical as well as atypical features such as psychiatric presentations, mimicking depression or schizophrenia, with few or subtle neurologic signs, beginning in adoles- cence or adulthood. A severe form of NPD type C presents at birth with ascites, jaundice, and a rapidly progressive fatal course. NPD type D was described among the French Acadians in Nova Scotia (Canada) with a disease onset usually between age 2 and 4 years. A founder mutation in NPC1 has subsequently been described in this population. MRI of the brain is usually normal until the late stages of the illness. Eventually marked atrophy of the superior/anterior cere- bellar vermis, thinning of the corpus callosum, and mild cerebral atrophy is seen. Increased signal in the periatrial white matter, reflecting secondary demyelination, may also occur. Management of patients with NPD type C is primarily symptom- atic. Medical management of seizures, dystonia, and cataplexy is in- dicated. If disordered sleep is identified, a nocturnal sedative may be used. Supportive care includes chest physical therapy with aggres- sive bronchodilation, antibiotic therapy for intercurrent infection, physical therapy, and a regular bowel programme to prevent severe constipation, which may present as increased seizure frequency or increased spasticity. Swallowing must be monitored to allow con- sideration of gastrostomy tube placement when aspiration or nutri- tional compromise is imminent. Clinical studies have supported a role of iminogugar miglustat, n-butyldeoxynojirimycin, in stabilizing NPC. The agent has been approved for the management of neurologic manifestations of NPC in several countries, not including the United States. Preliminary studies of neurosteroid replacement therapy or the active agent which was the vehicle, hydroxypropyl β-cyclodextrin have shown some promise. Metachromatic leucodystrophy (sulphatide lipidosis) See ‘Leucodystrophies’, this chapter. Krabbe disease (globoid cell leucodystrophy) See ‘Leucodystrophies’, this chapter. Mucopolysaccharidoses (for individual discussion
see Chapter 12.8) The MPSs are a group of heterogeneous disorders resulting from deficiency of lysosomal glycosidases and sulphatases involved in the sequential degradation of glycosaminoglycans (GAGs). Each follows an autosomal recessive inheritance pattern except MPS II, which is X-linked. Their collective incidence is estimated at about 1 in 25 000 to 1 in 50 000. Incomplete hydrolysis and accumulation of GAGs leads to deposition of different types of intralysosomal in- clusion bodies in tissues, the most characteristic of which are the zebra bodies. Increased urinary excretion of the substrates dermatan sulphate, heparan sulphate, keratan sulphate, and chondroitin sul- phate is often used as a screening test for MPS in suspected cases; however, a definitive diagnosis of a particular MPS subtype is based

 on specific enzyme assays using plasma, leucocytes, or cultured skin fibroblasts. Despite being aetiologically distinct, several nonneurological clinical features are shared by MPSs, mainly coarse facial features and dysostosis multiplex. The latter refers to the typical skeletal and radiographic findings (e.g. bullet-shaped phalanges), and flattening and anterior beaking of the vertebral bodies. Ophthalmic compli- cations include corneal opacity, pigmentary retinal degeneration, optic atrophy, and glaucoma. Developmental regression is noted in several MPS subtypes. Hydrocephalus can result from the deposition of GAGs and histiocytic infiltration in the meninges (i.e. pachymeningitis). GAG storage at various sites may lead to nerve compression syndromes such as carpal tunnel syndrome and spinal cord compression. Following clinical suspicion, the first step in diagnosis a MPS dis- order is to measure urinary glycosaminoglycans. Neither the quan- titative nor the qualitative method can diagnose a specific lysosomal enzyme deficiency, including MPS I; however, an abnormality detected by either or both methods indicates the likely presence of an MPS disorder. Diagnosis is

confirmed by identification of biallelic pathogenic variants in respective genes by molecular sequencing or detection of deficient activity of the respective lysosomal enzyme in fibroblasts, leucocytes, or plasma. Children and adults with MPS invariably require intensive multi- disciplinary management which includes disciplines of genetics, neurology, cardiology, pulmonology and sleep medicine, ENT, Ophthalmology, surgery, orthopaedics, physical therapy, occupa- tional therapy, and speech therapy. Mucopolysaccaridosis I (MPS I) Mucopolysaccharidosis type I (MPS I), a progressive multisystem disorder caused by biallelic pathogenic mutations in IDUA leading to deficient activity of the lysosomal enzyme α-L-iduronidase. Clinical features range over a wide continuum, with affected individuals best described as having either severe or attenuated MPS I, a distinction that influences therapeutic options. The greatest variability is ob- served in individuals with attenuated MPS I. MPS I is seen in all ethnicities at a frequency of approximately 1:100 000 for the severe form and 1:500 000 for the attenuated form. Neurological features are consistent with severe MPS I (Hurler syndrome) whereas they are mild or absent in attenuated MPS I (Scheie syndrome). Deficiency of α-L-iduronidase removes nonreducing terminal α- L-iduronide residues during the lysosomal degradation of the glyco- saminoglycans heparan sulphate and dermatan sulphate. Heparan sulphate is found in abundance in the brain as part of the extracel- lular matrix. In MPS I, the accumulation of glycosaminoglycan in the lysosomes of neurons and secondary deposits of glycolipids that form zebra bodies presumably lead to severe intellectual disability and hydrocephalus. In severe MPS I, infants appear normal at birth but may have in- guinal or umbilical hernias. The mean age of diagnosis for severe MPS I is approximately nine months. Death is caused by cardio- respiratory failure usually within the first ten years of life. Systemic features include coarsening of facial features, hepatosplnomegaly, progressive skeletal dysplasia (dysostosis multiplex), corneal clouding, hearing loss and cardiac involvement with thickening and stiffening of the valve leaflets can lead to mitral and aortic re- gurgitation. Chronic recurrent rhinitis and persistent copious nasal discharge without obvious infection are common. Noisy breathing and obstructive sleep apnoea is caused by storage of GAGs that is associated with enlargement of the tongue, tonsils, and adenoids, narrowed trachea, and thickened vocal cords. Normal early neurological development is followed develop- mental delay, usually obvious by 18 months.
A measurable decrease in intellectual capacity occurs thereafter. Language skills are limited due to the triad of intellectual decline, hearing loss, and large tongue. Children may plateau for several years followed by a slow decline in intellectual capabilities. By the time of death at age 8–10 years, most children are severely intellectually disabled. Communication hydro- cephalus is common. Definitive therapy with haematopoietic stem cell transplant (HSCT) is considered standard of care for children with severe MPS I. Outcome from HSCT is significantly influenced by disease burden at the time of diagnosis. It is generally recommended that HSCT be performed before age two years to maximize benefit. In children undergoing HSCT before evidence of significant developmental delay (i.e. usually between ages 12 and 18 months), HSCT appears to slow the course of cognitive decline. Children showing significant cognitive impairment prior to undergoing HSCT do not show cor- rection of existing impairment. Although an approved ERT exists for MPS I, it does not cross the blood–brain barrier and thus is not ex- pected to influence the CNS disease in severely affected individuals. Mucopolysaccaridosis II (MPS II) Mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) is an X-linked multisystem disorder characterized by deficiency if iduronate 2-sulphatase (I2S) leading to glycosamino- glycans (GAG) accumulation in several organs and consequently varied clinical presentations related to these organs. CNS involvement is significant in the group of children labelled as ‘early progressive’ disease, manifesting primarily as progressive cognitive deterioration. Cognitive decline, combined with the pro- gressive airway and cardiac

disease, usually results in death in the first or second decade of life. In the slowly progressive form, the CNS is minimally affected, if at all. Survival into the early adult years with normal intelligence is common in this group. The appearance of newborns with MPS II is normal. Coarsening of facial features and macroglossia generally manifests between ages 18 months and four years in the early progressive form and about two years later in the slowly progressive form. CNS manifestation is inexorable, usually resulting in developmental regression between ages six and eight years. Chronic communicating and seizures may also occur. Growth in the first five years of life may be above average fol- lowed by growth lags and eventual short stature. Macrocephaly is universal. Ivory-coloured skin lesions on the upper back and sides of the upper arms are pathognomonic of Hunter syndrome. Hypertrophic adenoids and tonsils and ankylosis of the temporo- mandibular joint limits opening of the mouth and may lead to pro- gressive swallowing impairment. Hoarse voice, irregularly shaped teeth, overgrown gingival tissue, painful dentigenous cysts, and conductive and sensorineural hearing loss, complicated by recur- rent ear infections, occur in most affected individuals. Joint contrac- tures, particularly of the phalangeal joints, causing significant loss of joint mobility are one of the earliest noteworthy diagnostic clues. Hip dysplasia is the most common long-term orthopaedic problem

section 24 Neurological disorders 6230 and can become a significant disability with early onset arthritis if not treated. Respiratory involvement hasis multifactorial: frequent upper-respiratory infections, airway obstruction, thickof respiratory secretions, and stiffness of the chest wall. Progressive obstructive airway disease results in sleep apnoea, the need for positive pressure assistance and eventually tracheostomy. Valvular heart disease is common; cardiomyopathy, hypertension, and rhythm disorder are seen occasionally. Hepatomegaly and/or splenomegaly and umbil- ical/inguinal hernia are frequent findings. A recombinant form of human iduronate 2-sulphatase that has been approved in the United States and the European Union for the treatment of MPS II and has shown efficacy in ameliorating some systemic manifestations of MPS II. However, it does not cross the blood–brain barrier and therefore, CNS manifestations are unchanged. Mucopolysaccaridosis III (MPS III) MPS III or Sanfilippo syndrome is due to an abnormal accumula- tion of heparan sulphate secondary to defective degradation within the cell. MPS III is divided into the following five subtypes based on the different enzyme deficiencies: (1) MPS IIIA (heparan-N-sulphatase), (2) MPS IIIB (α-N-acetylglucosaminidase), (3) MPS IIIC (acetyl-coenzyme A: α-glucosaminide acetyltransferase), (4) MPS IIID (N-acetylglucosamine-6-sulphatase) and (5) currently putative MPS IIIE (N-glucosamine 3-O-sulphatase, arylsulfatase G or ARSG). The incidence of MPS III or Sanfilippo syndrome ranges from 0.29/100 000 to 1.89/100 000 live births. Systemic features are similar to other MPS disorders such as coarse facial features, skeletal pathology, stunted growth, hepatosplenomegaly, macrocrania, and hearing loss. However, the primary characteristic feature of MPS III is de- generative CNS disease resulting in mental retardation and hyper- activity, typically commencing during childhood. Pre-natal and early stages of post-natal development are usually normal. The ini- tial stages of disease may begin between the ages of 1 and 3 years, which manifest as delayed cognitive development and/or aggressive behavioural problems such as hyperactivity with violent destructive behaviours and sleep disturbances, as well as hindered speech devel- opment which may become increasingly severe between the ages of 3 and 5 years. Patients may plateau between 5 to 10 years of age fol- lowed by neuroregression with a progressive and severe loss of intel- lectual processes and motor functions. MPS III patients ultimately regress to a vegetative state until death, which can occur anywhere between the early teens to late adulthood. Glycoproteinoses Deficiency of lysosomal

exoglycosidases involved in the hydrolysis of the carbohydrate side chains attached to the peptide backbone of glycoproteins by the N-glycosidic asparagine links leads to dis- orders of glycoprotein degradation termed the ‘glycoproteinoses’. All are sautosomal recessive in inheritance. The clinical features of glycoproteinoses are similar to the MPS disorders, such as coars- ening of facial features, dysostosis multiplex, intellectual impair- ment, and hepatosplenomegaly. Patients with glycoproteinoses have excessive urinary excretion of oligosaccharides; however, identifi- cation of the underlying enzyme deficiency requires assays use of leucocytes or cultured skin fibroblasts. Mannosidosis Mannosidosis results from a deficiency of either α- or β- mannosidase. MAN2B1 is the only gene known to be associated with α-mannosidosis. Glycoproteins are digested by proteinases and glycosidases within the lysosomes into small fragments to be excreted or transported to the cytosol for reuse. Lack of lysosomal α-mannosidase, results in the multisystemic accumulation of un- digested oligosaccharides in the lysosomes. Three clinical forms of α-mannosidosis are distinguished based on the age of onset. The more severe infantile form (type III) is associated with severe mental deterioration, facial dysmorphism, dysostosis multiplex, and hepatosplenomegaly, with death occurring usually between the ages of 3 and 10 years often due to infection. In the relatively milder type II form intellectual impairment is evident by 2 or 3 years of age with delayed speech and poor motor performance. There are superficial corneal opacities, spoke-like posterior lens opacities, deafness, subtle facial dysmorphism, and skeletal abnormalities on radiographs. The clinical course is protracted, extending into adulthood. Late neurological complications include hydroceph- alus and spastic quadriplegia. Widening of the diploic space with underdevelopment of the sinuses and prominent periventricular Virchow–Robin spaces are seen on MRI of the brain. Destructive arthropathy due to storage of oligosaccharides may be seen in chil- dren and adults. A mild form (type I) is recognized after age ten years with absence of skeletal abnormalities, myopathy, and slow progression. The lysosomal enzyme β-mannosidase cleaves the β-linked man- nose residue present in all types of N-glycosylprotein glycans. Clinical spectrum is variable and given the low incidence of the disease a de- fined phenotype is difficult to establish. However, β-Mannosidosis presents with a range of neurological features including severe psy- chomotor retardation, hearing loss, seizures, peripheral neuropathy. The diagnosis of mannosidosis relies measurement of respective mannosidase enzyme activity in peripheral blood leukocytes or other nucleated cells such as fibroblasts. Gene sequencing helps demonstrate two pathogenic mutations. No definitive therapy is available. Fucosidosis Deficiency of α-fucosidase leads to accumulation of fucose- containing oligosaccharides, glycopeptides, and, to a lesser extent, mucopolysaccharides and glycolipids in tissues associated with their excessive urinary excretion. There is prominent neurological dys- function in all subtypes. The early onset severe infantile form (type I) with neurological deterioration between 6 and 18 months of age rapidly progresses to a decerebrate state. Associated features are coarse facies, growth retardation, recurrent infections, dysostosis multiplex, angiokeratoma. The later-onset form is relatively slowly progressive (type 2); neurological regression occurs in the second or third year of life. Death usually occurs between the ages of 4 and 6 years in both subtypes. A third group of patients may show slowly progressive neurological deterioration into adolescence or adult- hood. Brain MRI shows extensive and progressive changes in the signal intensity of the white matter and the internal medullary lam- inae of the thalami, as well as high signal intensity on T1-weighted images and low signal intensity on T2-weighted and FLAIR images in the globus pallidus and substantia nigra. The diagnosis is based

 on demonstration of decreased α-fucosidase activity in leucocytes or cultured skin fibroblasts. Aspartylglucosaminuria Aspartylglucosaminuria is

described largely in Finland and results from a deficiency of aspartylglucosaminidase (AGA). This enzyme cleaves the bond between asparagine and N-acetylglucosamine of N-linked glycoproteins. Speech problems and severe behavioural abnormalities, with alternating periods of hyperactivity and ap- athy, are predominant in the clinical picture. Recurrent infections and diarrhoea are common in the early months and years of life. Insidious motor and mental deterioration, often with seizures, de- velop between the ages of 5 and 15 years. Mild coarsening of the fa- cial features and skeletal abnormalities such as deformities of the vertebrae, periosteal thickening of the long bones, and thickening of the calvarium are evident by adolescence. Increased aspartylglucosamine in urine and decreased AGA ac- tivity in plasma, leucocytes, or cultured skin fibroblasts confirm the diagnosis. Sialidosis Sialidosis types I and II are clinical variants associated with the defi- ciency of α-neuraminidase (sialidase, NEU1) and increased urinary excretion of sialyloligosaccharides. A few vacuolated lympho- cytes and histiocytes may be present in peripheral blood and bone marrow smears, respectively. At the ultrastructural level swollen lysosome are visible in bone marrow cells and in Kupffer cells of the liver. Increased high molecular weight sialylated oligosaccharides are found in the urine. In sialidosis type I (cherry red spot–myoclonus syndrome) pro- gressive visual loss with a typical eye finding of a macular cherry red spot, myoclonus, and seizures develop in late childhood or ado- lescence, usually by the second or third decade. Typically, these patients have no obvious physical defects, and their intelligence is normal or only slightly impaired. Most prominent clinical finding is irregular myoclonic jerks. They are precipitated by action, sensory stimuli, emotional upset, menstruation, and smoking. The visual loss is progressive and is associated with bilateral macular cherry red spots that may fade later in the course of the disease. The progres- sive nature of the disease leads to difficulties with speech, walking, and feeding, followed by blindness, optic atrophy, and intellectual deterioration. Brain imaging shows cerebral and cerebellar atrophy. In sialidosis type II, also known as mucolipidosis type I has an in- cidence of 0.02/100 000 live births. There are neurological, visceral, and skeletal abnormalities including dysostosis multiplex, a Hurler- like phenotype, intellectual impairment, and hepatosplenomegaly. There are three sub types: the congenital form, with onset in utero, is associated with nonimmune hydrops fetalis, ascites, facial oedema, inguinal hernias, and hepatosplenomegaly. They are stillborn or die shortly after birth with a systemic and fulminant condition. Both the infantile patients with longer survival and the juvenile cases de- velop macular cherry red spots and myoclonus, and may also have hearing loss and angiokeratoma. The diagnosis is based on deficient α-neuraminidase activity, preferably in cultured skin fibroblasts or leucocytes. Galactosialidosis results from the combined deficiency of α- neuraminidase and β-galactosidase, due to defects in the protein cathepsin A (PPCA), which offers protection against rapid proteo- lytic degradation. It is clinically characterized by cerebellar ataxia, myoclonus, and visual failure in late childhood or adolescence. Additional features include the cherry red macular spot, dysmorphic facial features, hepatomegaly, and skeletal changes. The diagnosis of galactosialidosis is based on deficient activity of both α-neuraminidase and β-Gal in leucocytes or cultured skin fibroblasts, and/or mutations in the gene encoding the PPCA. Galactosialidosis can be distinguished from GM1 gangliosidosis by normal β-Gal activity in serum or plasma, unlike GM1 gangliosidosis. Schindler’s/Kanzaki’s disease (a-N- acetylgalactosaminidase deficiency) This rare disorder, initially described by D Schindler, is a form of neuroaxonal dystrophy, which results from deficiency of a glycosyl- hydrolase, α-N-acetylgalactosaminidase (NAGA). Progressive motor and mental deterioration, with myoclonic seizures, pyram- idal signs with hyperreflexia, hypotonia, and optic atrophy were described in two brothers who were bedridden by age 4 years. Subsequently, in 1989, Kanzaki and colleagues described a group of adult Japanese patients, without overt

neurological manifest- ations and diffuse angiokeratoma, who had NAGA deficiency and increased urinary excretion of several glycopeptides. Mucolipidoses The mucolipidoses feature the combined tissue storage of GAGs and sphingolipids and are a group of disorders with clinical fea- tures similar to MPSs, except for the absence of urinary excretion of GAGs. Mucolipidosis type I or sialidosis type II This condition is described under ‘Sialidosis’, this chapter. Mucolipidosis type II and type III Mucolipidosis type II (I-cell disease) and type III (pseudo-Hurler’s polydystrophy) are caused by is caused by a mutation in the N-acetylglucosamine-1-phoshate transferase, α/β subunits (GNPTAB) gene. This results in abnormal transport of newly synthesized enzymes to the lysosome due lysosomal acid hydrolase enzymes lacking a normal recognition phosphate group and abnormally accumulating in the extracellular space rather than the lysosome. Mucolipidosis II has autosomal recessive inheritance, with a world- wide prevalence of 0.15/100 000 live births. I-cell disease manifests with progressive severe psychomotor retardation, dysmorphic facial features, gingival hypertrophy, and dysostosis multiplex. Cardiorespiratory abnormalities are similar to those seen in MPS I (Hurler syndrome), including cardiac valve problems, thick- ening of the airways, and thoracic cage stiffening. ML-III has a similar clinical picture; in addition to stiffness of the fingers and shoulder, a ‘claw-hand’ deformity, short stature, and scoliosis may be noted. Mild coarsening of the face, corneal clouding, and ret- inopathy with progressive bone and cardiac valve involvement are also commonly seen. The diagnosis of ML-II and -III is based on a demonstration of markedly increased lysosomal enzyme activities in the plasma while the corresponding activities in leucocytes and cultured skin fibroblasts are markedly decreased.

section 24 Neurological disorders 6232 Mucolipidosis type IV Mucolipidosis IV (ML-IV) is caused by mutations in the gene MCOLN1, mapped to chromosome 19p13.3–13.2. It encodes pro- tein called mucolipin, which normally functions as a calcium (Ca2+)- permeable cation channel but is also involved in lysosomal biogenesis and membrane trafficking. ML-IV is prevalent among the Ashkenazi Jewish population with two common mutations accounting for 95% of the alleles. However due to aggressive premarital couple screening, currently most affected individuals are non-Ashkenazi Jewish. The disease has a protracted course characterized by early arrest in neurological development by the end of first year of life manifesting as absent speech, intellectual impairment, and motor retardation and slowly progressive visual impairment during the first decade as a result of a combination of corneal clouding and retinal degeneration. Achlorhydria is a consistent manifestation which may lead to iron deficiency and iron deficiency anaemia. Progressive renal failure has been recognized in recent years to be a feature of MLIV. There are no dysmorphic facial features, hepatosplenomegaly, or skeletal abnor- malities. Neurologic examination typically reveals severe dysarthria or anarthria, slow chewing, slow eating and swallowing, spasticity, and hyperactive tendon reflexes. Diagnosis may be based on electron microscopic examination of conjunctival and skin biopsies which show characteristic lysosomal inclusions as well as enlarged lysosomes in all cell types. However, molecular genetic analysis of common mutations is often used for diagnostic purposes. Speech therapy, physical therapy for spasticity and ataxia, ankle– foot orthotics (AFOs), antiepileptic drugs as needed, and surgical correction of strabismus are employed for supportive care. Eye care includes topical lubricating eye drops, artificial tears, gels, or oint- ments for ocular irritation. Glycogen storage disease type II (Pompe disease) Pompe disease, also known as (PD, OMIM 232300) glycogen storage disease type II and acid-maltase deficiency, is a metabolic myopathy characterized by lysosomal glycogen storage caused by deficiency of the lysosomal enzyme acid α-glucosidase. Pompe disease has a varied estimated frequency in different ethnicities of one in 40 000 in African-American to 146 000

in Australian populations. The gene-encoding acid α-glucosidase (GAA) is mapped to chromosome 17q and contains 19 coding exons. Over 200 muta- tions have been reported, of which about 75% are pathogenic. When the acid α-glucosidase activity decreases below critical, lysosomal glycogen begins to accumulate. This glycogen is not primarily util- ized for energy production and therefore common manifestations seen in other glycogen storage disorders of hypoglycaemia, ketosis, or lactic academia are not seen in PD. This threshold level of enzyme required to accumulate glycogen varies depending on the organ. Hypertrophic cardiomyopathy is a typical sign of classic infantile Pompe's disease in which no residual acid α-glucosidase activity is present, but is rarely seen in late-onset forms with higher residual activity. Pathological changes in skeletal muscle, however, are prom- inent throughout the clinical spectrum. Pompe disease may present at any age, though the classic in- fantile form was first described by Pompe in 1932 and usually pre- sents in patients within the first months of life with median age of onset between 1.6 to 2.0 months. Presenting symptoms are feeding difficulties, failure to thrive, respiratory infections, hypotonia, and diminished spontaneous movements. The heart is characteristically affected with hypertrophic cardiomyopathy, thickening of the ven- tricular walls and septum that may lead to outflow tract obstruc- tion and cardiac failure. The electrocardiogram shows high voltages, repolarization disturbances, and frequently a short PR interval. Motor development is delayed and major motor milestones such as rolling over, sitting, or standing are usually not achieved. Patients show slipping through on vertical suspension and prom- inent head lag. Tendon reflexes are often diminished. There is en- largement of the tongue and the liver. Hearing deficit, osteoporosis and osteopenia are now noted as a features in children who survive longer following administration of enzyme replacement therapy. Prior to ERT mean age of death was 6.0–8.7 months; patients with classic infantile Pompe's disease rarely survive beyond 1 year of age. With onset beyond one year of age, cardiac involvement is much milder or absent. Symptoms of children and adults with a non- classic presentation are predominantly related to skeletal muscle dysfunction, resulting usually in reduced mobility followed by re- spiratory problems. Presenting symptoms are difficulty running, climbing stairs, rising from an armchair, and walking. Other first symptoms were fatigue and muscle cramps. Early involvement of the diaphragm leads to low vital capacities in the supine position al- though pulmonary function in the upright position is still adequate. This leads to sleep disordered breathing and patients learn to sleep with their head elevated. Patients may report morning headache as a symptom of hypoventilation during sleep causing hypercarbia. Use of accessory muscles such as sternocleidomastoid may be evident during clinical examination. Patients who are still ambulatory may need ventilation at night. Patients progress slowly but relentlessly to loss of ambulation and wheel chair use along with ventilator sup- port. Life expectancy is diminished in juvenile and adult patients with Pompe disease, usually related to pulmonary complications. Late-onset forms of Pompe closely mimic limb-girdle muscular dys- trophy in presentation and often may be diagnosed in that category. The average diagnostic delay ranges from 7 to 10 years; although nu- merous cases are known where diagnosis is delayed for decades. Very high index of suspicion is necessary to ensure timely and appropriate diagnosis, given that enzyme replacement therapy is now available. Diagnosis is confirmed by enzyme estimation in peripheral leuco- cytes or isolated lymphocytes. Several new methods use assays of acid α-glucosidase activity in dried bloodspots which offers a convenient and reliable method for screening. Infants with classic Pompe dis- ease have less than 1% residual activity; children and adults have residual activity, but usually no more than 30% of average normal activity. Sequencing the GAA gene provides confirmation of diag- nosis by identifying the mutations as well providing family mutation for screening other family members for affected or carrier state. ERT was first approved in Europe and United States

for infantile and late onset forms of PD in 2006. In infantile PD, ERT should be initi- ated as soon as the diagnosis of infantile Pompe disease is established. Infusion associated reactions are common, which can be modified by slowing the rate of infusion or administration of antipyretics, anti- histamines, or glucocorticoids. Majority of treated children develop IgG antibodies to ERT within the first three months of treatment. Affected individuals with high sustained IgG titers may have a poor clinical response to treatment. Infants who are CRIM (cross-reactive immunogenic material) negative require immunomodulation very

24.17 Inherited neurodegenerative diseases 6233 early in the treatment course, optimally before the first infusion. Compared to an untreated cohort, when ERT is initiated before age six months and before the need for ventilatory assistance there is im- proved survival, improved ventilator-independent survival, reduced cardiac mass, and significantly improved acquisition of motor skills. Treatment with alglucosidase alfa reduces the risk of mortality in late-onset patients to close to a fifth of that experienced in the natural course. Patients on treatment demonstrate improved pulmonary function as documented by forced vital capacity (FVC) within the first few months, followed by a gradual return to baseline in con- trast to the consistent decline and earlier death seen in untreated pa- tients. Over time the difference in percentage predicted sitting FVC between treated and untreated patients increases. Improvements in the six minute walk test occur quickly and are sustained over time. Sialic acid storage disorders These autosomal recessive disorders, caused by mutations in the sialin gene, SLC17A5, encoding a protein involved in the transport of sialic acid (N-acetylneuraminic acid), include the following allelic disorders: infantile free sialic acid storage disease (ISSD) and Salla's disease (or the Finnish variant). The severe infantile form (ISSD) presents with nonimmune hydrops, hypertrophic cardiomyopathy, ascites, hepatosplenomegaly, inguinal hernias, coarse facies, and dysotosis multiple, causing death in the first 2 years of life. Clinical features of the juvenile form include developmental delay and growth retardation, seen in early childhood with mild coarsening of the facial features, hepatomegaly, and psychomotor retardation. In Salla's disease, named after a region in northeastern Finland, af- fected children manifest with mild coarsening of features, exotropia, hypotonia, ataxia, and learning disabilities during the first year of life without visceromegaly or skeletal abnormalities. Increased amounts of free sialic acid are found in the serum and urine, as well as in cultured skin fibroblasts and several tissues, including the brain. Neuronal ceroid lipofuscinoses (NCLs) The neuronal ceroid lipofuscinoses (NCLs) represent a group of childhood-onset disorders with a combined prevalence of approxi- mately 1 in 12 500 births characterized by the intralysosomal aggre- gation of autofluorescent proteinaceous ageing pigments (i.e. ceroid and lipofuscin). Under the electron microscope, the accumulated material takes three different forms: granular osmiophilic deposits (GRODs), curvilinear profiles, and fingerprint bodies. The form that predominates in a particular patient correlates with the particular mutated gene. For example, in CLN1 only GRODs are seen and in CLN2 curvilinear profiles predominate, whereas CLN3 is distin- guished by a preponderance of fingerprint bodies. They share common clinical features that include epileptic seiz- ures, progressive psychomotor decline, visual failure, and premature death. There are eight major subtypes based on age at onset, pres- entation, and pathological findings (CLN1, CLN2, CLN3, CLN5, CLN6, CLN7, CLN8, and CLN10). Clinical progression varies among the different NCLs. There are an increasing number of ex- amples of different mutations in a single gene giving rise to quite dif- ferent diseases (e.g. a particular missense mutation in CLN2/TPP1 is associated with spinocerebellar ataxia SCAR7, a slowly progressing but not life-limiting disease with no ophthalmologic abnormalities or epilepsy, and absence of typical storage). Diagnosis is established

by demonstration of the respective en- zyme deficiencies in peripheral leucocytes or cultured fibroblasts. Diagnosis is significantly aided by electron microscopy of a skin bi- opsy and observation of nerve endings that show the typical inclu- sions. It is recommended that skin biopsy be obtained from sensitive skin areas such as the axilla where the density of nerve endings may be higher. Molecular testing establishes the diagnosis with biallelic mutations detected. CLN1 The infantile form of NCL, caused by mutations in CLN1, the gene encoding the enzyme palmitoyl-protein thioesterase 1 (PPT1), has the widest range of age of onset. PPT1 removes palmitate residues from proteins which accumulate in CLN1 as GRODs. Whichever the age of onset, all CLN1 patients will have GRODs on electron microscopy. Palmitoylation plays a critical role in neuronal vesicular transport and intracellular signalling. PPT1 is also found in non- lysosomal compartments in presynaptic terminals. These findings suggest that CLN1 is may not exclusively be a storage disorder. Most patients have infantile onset between 8 and 18 months of age with irritability, deceleration of head growth, muscular hypo- tonia, ataxia, motor clumsiness, irritability, sleep disturbance, and visual failure after a period of normal development during the first year. Rapid developmental deterioration occurs during the second year of life with loss of all motor abilities and social interest, blind- ness, and increasing spasticity, seizures, and myoclonus. Fine motor skills are affected with purposeless, characteristic hand movements (hyperkinesias) such as those seen in Rett's syndrome. Death usually occurs in early childhood. Some patients may have late-infantile, ju- venile, and even adult-onset as late as 40 years of age. It is possible that most if not all Kuf's disease (originally CLN4) cases are actually adult-onset CLN1. CLN2 Cerliponase alfa was the first drug to be approved by US FDA in April 2017 for treatment of TPP1 deficiency in pediatric patients over three years of age. Clinical studies showed that intraventricular enzyme replacement therapy with recombinant TTP1 administered every other week slowed the loss of walking ability in treated pa- tients as compared with a natural historical cohort. Late-infantile NCL, caused by mutations in CLN2, which encodes the enzyme tripeptidyl-peptidase 1 (TPP). The enzyme removes tri- peptides from N-termini of small proteins such as the subunit c of mitochondrial ATP synthase. In addition to the lysosome, TPP1 lo- calizes to the Golgi apparatus, lipid rafts, and endosomes, and inter- acts with CLN5, CLN3, and CLN8. Presence of pure curvilinear membrane-bound lysosomal aggregates without clear lipid droplets is the hallmark for CLN2 mutation disease. Onset is between second and fourth year of life with unexpected delay of psychomotor development or epilepsy of sudden onset. Seizures are generalized tonic-clonic or partial, frequently of a severe myoclonic type, which may soon become resistant to drug treatment. Gross and fine motor abilities, cognitive functions, and, later, vision are rapidly lost within 3 years of onset. Spasticity, truncal hypotonia, loss of head control, near-continuous myoclonus, frequent seizures, and an extended vegetative state characterize the rest of the child's life until death in early adolescence. Death is often due to aspiration pneumonia. Electroencephalography (EEG) includes characteristic

section 24 Neurological disorders 6234 occipital spike responses to slow flash (1–2 Hz) stimulation before the onset of seizures, which exaggerates as the disease progresses. Electroretinography is diminished even before noticeable visual loss. CLN3 Juvenile NCL, caused by mutations in CLN3. Ultrastructurally, CLN3 cases exhibit fingerprint profiles within the lysosomal re- sidual body, or in conjunction with curvilinear or rectilinear profiles, or as a small component within large membrane-bound lysosomal vacuoles. CLN3 encodes a transmembrane protein that has been reported to localize to membrane lipid rafts in lysosomes, endosomes, synaptosomes, and the cell membrane, as well as in mitochondria. CLN3 has been implicated in antiapoptosis, pro- cessing of mitochondrial membrane proteins, regulation of lyso- somal pH, transport of basic amino acids into

the lysosome, and lysosomal size. CLN3 presents with visual failure, noticed around the age of 5 to 10 years leading to blindness usually within a few years, gradual psychomotor deterioration during early school years, followed by seizures and psychosis. Ocular pathology is initially a pigmentary retinopathy often misdiagnosed as retinitis pigmentosa or cone dys- trophy. In adolescence, speech, mobility, and cognitive skills deteri- orate and seizures set in. Children have behavioural problems such as aggressiveness, psychosis, mood disturbance, and anxiety. Speech becomes dysarthric and dysfluent with echolalia. As the disease pro- gresses, myoclonic jerks and parkinsonian features and gait develop. This particular NCL is diagnosable through the identification of vacuolated blood lymphocytes. CLN5 Mutations in CLN5 cause the Finnish variant of late-infantile NCL with onset between four and 7 years. CLN5 encodes a transmem- brane protein and is synthesized as four precursors, all directed to the lysosome. The longest form is associated with the lysosomal membrane and interacts with CLN2 and CLN3. Lipopigments are distributed in the central nervous system and extracerebrally, and include fingerprint bodies, curvilinear profiles, lamellar inclusions, and occasionally condensed fingerprint figures associated with lipid droplets. Characteristic clinical symptoms include developmental regres- sion, visual impairment, ataxia, and myoclonus epilepsy, similar to the other NCLs. Neurophysiologic examination shows giant visual-evoked potentials, exaggerated somatosensory potentials, and occipital spikes in response to photic stimulation, similar to CLN2. CLN6 CLN6 encodes a protein of unknown function with seven trans- membrane domains localizing to the endoplasmic reticulum. Lipopigments include fingerprint, curvilinear, as well as rectilinear patterns. CLN6 is found in multiple ethnicitieswith age of onset ran- ging from 18 months to 8 years, with the majority between 3 and 5 years. Early features include gait and speech disturbance, seizures, and developmental delay. CLN7 The CLN7 gene product is a lysosomal integral membrane pro- tein with features suggestive of transport function. In CLN7 dense fingerprint profiles are present in the lymphocytes. Disease onset is between 2 and 7 years. Psychomotor regression or seizures can be the initial presenting signs. CLN8 The CLN8 protein appears to be an enzyme in the pathway of ceramide synthesis and localizes to the ER and the ER–Golgi inter- mediate compartment. GROD, curvilinear, and fingerprint pro- files have been reported on electron microscopy, in various tissues, including lymphocytes. CLN8 has two forms based on the muta- tion: childhood-onset (5–10 years) with intractable epilepsy fol- lowed by progressive cognitive decline or mild developmental delay in infancy followed by a florid progressive myoclonic epilepsies (PME) with progressive myoclonus, seizures, retinopathy, and psy- chomotor regression starting between three and six years. CLN10 CLN10 is a fulminant disease due to mutations in lysosomal pro- tease, cathepsin D, where complete loss-of-function mutation leads to a congenital form with encephalopathy, status epilepticus, and death due to respiratory insufficiency in the first days and weeks of life with massive GRODs in the central nervous system. Milder form with missense mutations in one patient is described with childhood-onset neurodegenerative disease with ataxia, retinop- athy, severe cognitive decline, and no seizures at age 17. Section IV Dementia syndromes Almost all major dementia syndromes are disorders of abnormal protein aggregation. Both genetic and sporadic forms of each illness exist and overlap has been found with parkinsonian–dementia syn- dromes. This section surveys the clinical genetics of dementia. See Chapter 24.4.2 for more detailed clinical account of the dementing disorders. Alzheimer’s disease Alzheimer’s disease accounts for about two-thirds of cases of pro- gressive dementia. It begins with the insidious onset of loss of re- cent memory, increasing forgetfulness, disorientation, decreased abstraction ability, and word-finding difficulty. Behavioural prob- lems arise including agitation, restlessness, insomnia, paranoia, and sometimes delusions or hallucinations. Depression is common. As the disease progresses the

patient becomes increasingly immobile, incontinent, and mute with death occurring one to two decades after symptom onset. Pathological hallmarks, in both familial and sporadic cases, are extracellular plaques of amyloid-β (Aβ) and intraneuronal inclu- sions of hyperphosphorylated tau within the cortex and subcor- tical nuclei. The neuritic plaques containing extracellular deposits of amyloid β-protein (Aβ) are intimately associated with dystrophic neurites, activated microglia within the amyloid deposit, and re- active fibrillary astocytes surrounding the lesion. The tangles consist of masses of abnormal paired helical filaments (PHFs) and straight filaments in the perinuclear cytoplasm of selected neurons. The PHFs contain insoluble aggregates of the microtubule-associated protein tau in a hyperphosphorylated, largely insoluble form, often conjugated with ubiquitin. Fibrillar Aβ deposits are also found in the

24.17 Inherited neurodegenerative diseases 6235 basement membranes of cerebral capillaries, arterioles, and small arteries. Clustering of early onset Alzheimer's disease within families was observed as early as the 1930s. In the 1990s it was confirmed that the disease could be caused by autosomal dominantly inherited genetic mutations. Initially mutations were described in the amyloid pre- cursor protein (APP) gene on chromosome 21 and subsequently in presenilin (PSEN)1 on chromosome 14 and PSEN2 on chromo- some. Over 200 changes, including mutations, polymorphisms, and variants of unknown significance have now been described in these genes. Duplications of the APP gene as well as an extra copy as seen in Down's syndrome or trisomy 21, have also been identified as an additional cause of familial Alzheimer's diease (FAD). Mutations in PSEN1 account for most cases of FAD and collectively, FAD accounts for up to 0.5% of Alzheimer's in general. Though the mechanisms are complex and variable, all three genes known to cause FAD ultimately result in the enhanced production and/or deposition of Aβ. APP is a transmembrane protein that ap- pears to play a role in neural plasticity and the regulation of synapse formation. When APP is sequentially acted on by β- and γ-secretase, β- secretase activity generates a soluble extracellular fragment and its transmembrane domain is cleaved γ-secretase at a variety of different sites, generating a peptide from 39–43 amino acids in length: the Aβ protein. PSEN1 forms part of the γ-secretase complex. Aβ peptides, particularly Aβ42, may have toxic effects on neuronal and synaptic function intracellularly, and seed extracellularly to precipitate in the form of amyloid plaques. Most FAD-causing mutations appear to ei- ther increase Aβ40 and Aβ42, or alter the ratio between them. Both FAD and sporadic Alheimer's show a greater proportion of Aβ40 de- position in individuals who carry an ε4 allele. Additionally, possession of the APOε4 allele in FAD is associated with a decreased age at onset. Two distinct histopathological profiles identified in FAD caused by PSEN1 mutations are driven by the position of the mutation within the gene, although this is not absolute. Type 1 pathology, associated with mutations occurring before codon 200, closely resembles the pathology in sporadic Alzheimer's disease, with many diffuse and cored plaques, and few white-matter plaques. Amyloid angiopathy is mild to moderate, confined to leptomeningeal vessels. Mutations beyond codon 200 tend to have type-2 pathology, which is more severe leptomeningeal and intraparenchymal amyloid angiopathy with large diffuse plaques concentrated around amyloidotic arteries. Independent of the APOE genotype Aβ40 deposition is increased in those with type 2 pathology. Individuals with type 1 pathology have a younger age at onset (on average 5 years earlier) and shorter dis- ease duration (c.2.5 years) than those with type 2 pathology. It has been suggested that in addition to increasing the produc- tion and deposition of Aβ42 some mutations affect Notch signalling, inducing breakdown of the vascular epithelium causing leakage of Aβ into brain tissue. Seeding of existing deposits of Aβ may produce larger plaques seen around vessels in type 2 pathology and promote development of amyloid angiopathy.

Majority of the reported APP mutations lie in the vicinity of the β- and γ-secretase cleavage sites. Families with mutations at these sites were found to have, in addition to early impairment of episodic memory, dyscalculia, lack of insight, and prominent myoclonus and seizures. Mutations found within the Aβ coding sequence, have spe- cific relation to amyloid angiopathy The 'Dutch mutation' in APP, a glutamic acid to glutamine substitution at position 693 (APPE693Q) gives rise to severe amyloid angiopathy leading to recurrent cerebral haemorrhage. Pathologically, although diffuse parenchymal deposits of Aβ are present, neuritic plaques and neurofibrillary tangles are absent. Similar severe amyloid angiopathy is seen in patients with Iowa mutation (APP D694N) in addition to widespread neurofibrillary tangles and amyloid plaques, particularly abundant Aβ40 deposition. However, clinically patients presented with progressive cognitive impairment and not recurrent cerebrovascular events. Similarly, the 'Arctic' mutation APP E693G has a purely cognitive phenotype, despite the presence of marked amyloid angiopathy. Comparing the Arctic and Dutch mutations, which occur at exactly the same pos- ition (amino acid 693) but give rise to totally different phenotypes suggests that the polarity of the substituted amino acid influences the pathology. The Dutch mutation replaces glutamic acid with polar and hydrophilic glutamine, which may have a greater affinity for, and pro- pensity to disrupt, the vessel wall than the Artic mutation involves replacement with nonpolar and hydrophobic glycine. APP duplications Copy number variation plays a role in Alzheimer's disease patho- genesis as is well demonstrated by its association with Down's syn- drome. Duplications of the APP gene can give rise to FAD with diverse phenotype even within a single family. Pathologically prom- inent amyloid angiopathy and clinically high frequency of seizures are characteristic. The size of the duplication does not appear to influence the clinical presentation. The most striking feature of FAD is the younger age at onset compared to sporadic form: families with PSEN1 mutations present within the range 35 to 55 years, APP mutations between 40 and 65 years and PSEN2 mutations between 40 and 70 years. Majority of individuals with FAD have clinical presentations similar to sporadic Alzheimer's, comprising an early impairment of episodic memory with progressive involvement of multiple cognitive domains. However, several PSEN1 mutations have been reported to present with language impairment,. Posterior cortical atrophy described in sporadic Alzheimer's disease, with marked visual processing deficits and relatively well preserved memory, to date, has not been observed in FAD. Myoclonus and seizures, which are typically late manifestations in sporadic Alzheimer's, can be a particularly prom- inent and early sign in FAD. Spastic paraparesis, occurring simul- taneously with cognitive deficits or predating by several years, has been reported to occur in association with over 20 different PSEN1 mutations. Despite similar amounts of Aβ deposition in the cere- bellum, Purkinje cell loss and reactive astrocytosis are often more severe in FAD than sporadic Alzheimer's disease; cerebellar signs may be absent clinically. Extrapyramidal signs, particularly those causing very early onset of the disease, have been reported with several PSEN1 mutations. Of note, new light was shed on the role of innate immunity and in- flammation in development and progression of Alzheimer's disease when several groups reported a new pathogenic missense mutation in a gene coding for the triggering receptor expressed on myeloid- derived cells (TREM-2) and subsequently in CD33. TREM-2 is an innate immune receptor highly expressed on immature dendritic cells in the peripheral lymphatics, microglia, and osteoclasts. The receptor is normally involved in phagocytosis of neural debris in the brain and profoundly down-regulates proinflammatory cytokine production. Homozygous loss-of-function TREM-2 mutations

 have been previously linked to an early onset of dementia coupled with bone abnormalities. A heterozygous TREM-2 genetic variant is strongly associated

with a significant increase in the risk of late- onset Alzheimer's disease. The reduced function of TREM-2 in blocking proinflammatory cytokine production is thought to impair innate immune regulation and may be a key to the pathogenic risk of Alzheimer's disease. Frontotemporal dementia Frontotemporal dementia (FTD) is the second most common cause of presenile dementia, accounting for 12 to 25% of dementia cases with a prevalence estimated between 10 and 30 per 100 000 in indi- viduals between the ages of 45 and 65 years. Originally, the concept of FTD arose with the recognition of dementia with Pick's bodies (silver-staining intraneuronal inclusions) in the presence of circum- scribed atrophy of the frontotemporal regions. However, as Pick's bodies are present in a minority of cases, this finding is no longer an essential component of FTD. Almost 50% of individuals with FTD have a positive family history, and 10 to 20% conform to an auto- somal dominant pattern of inheritance (familial frontotemporal lobar degeneration FTLD). FTD presents in the sixth decade in three subtypes. In the frontal variant, behavioural changes predominate (bvFTD). Patients with predominantly left hemisphere involvement experience progressive language deficits (progressive nonfluent aphasia, PNFA). In cases of left anterior lobe atrophy, there is progressive loss of the know- ledge of words and objects, difficulties in communicative speech and understanding the semantic content of language (semantic de- mentia, SD). However, patients ultimately progress to more global impairment in frontal and temporal lobe functions. Pathologically, FTD is a proteinopathy characterized by presence of abnormal, ubi- quitinated protein inclusions that reside in the cytoplasm and nu- cleus of neuronal and glial cells. It is now recognized that FTLD and amyotrophic lateral scler- osis (ALS) co-occur on a spectrum of a disease complex. There is clustering of neurodegenerative diseases in relatives of patients with ALS. Up to half of ALS patients show some functional impairment in frontal lobe tests, and in 15% of cases it is severe enough to war- rant an official diagnosis of FTLD. On the other hand, around 40% of FTLD cases have measurable motor dysfunction with up to 15% meeting criteria for ALS diagnosis. Therefore, following terminology appropriately refers to patients as: (i) ALS with cognitive or behavioural impairment (ALS Ci/ALS Bi): ALS patients who do not meet the criteria for FTLD, but do have behavioural or cognitive deficits (ii) familial frontotemporal lobar degeneration and motor neuron disease (FTLD-MND or FTLD- MND-like): Patients with FTLD who show some motor neuron involvement clinically or on electromyography without actually developing ALS (iii) ALS-FTLD or FTLD-ALS: Those who fall at the midway point; the order is usually dependent on the clinical symp- toms that appeared first. Several genes are implicated in pure FTLD, FTLD-ALS, and pure ALS. Microtubule-associated protein Tau (MAPT) Originally FTLD families with autosomal dominant inheritance and clinical presentation of frontal disinhibition, dementia, parkin- sonism, and amyotrophy were linked genetically to chromosome 17q21, thus named FTDP-17 cases. Most of these FTDP-17 cases stained positive for inclusions of microtubule-associated protein Tau (MAPT). Analysis of the MAPT gene on chromosome 17q21 iden- tified the first novel missense and splice-site mutations in MAPT as- sociated with FTLD; subsequently 44 MAPT mutations have been reported that result are either missense mutation, interfere with al- ternative splicing, or disrupt the ratio of tau isoform. Mutations that disturb alternative splicing regulation lead to an increase in the four repeat (4R, sticky) form over three repeat (3R, nonsticky) form of tau, and along with missense mutations in exon 10 are associated with a tauopathy composed of 4R tau. Missense or splice-site mu- tations affecting exon 10 cause neuronal and glial inclusions while mutations outside of exon 10 cause neuronal inclusions only com- prised of all six isoforms. Progranulin Discovery of FTDP-17 families without MAPT mutations led to analysis of near-by genes, showing a second gene, granulin (GRN), within the region of chromosome17q21, 1.7 Mb centromeric to MAPT, which had mutations. Neuronal inclusions in these cases did not show tau-positive staining, but did

stain for ubiquitin. GRN gene encodes a cysteine-rich secreted glycoprotein, progranulin (PGRN), implicated in tissue repair, glucose sensing, and cancer. PGRN is proteolytically cleaved by enzymes such as elastase into small pep- tides, known as granulins. Most GRN mutations found to date cause disease due haploinsufficiency; nonsense mutations producing a premature termination of the coding sequence and a nontranslated protein. FTLD-ALS (also refer to ALS in Section X, Motor Neuron Disease) TDP-43 Most FTLD cases who had tau-negative inclusions but stained posi- tive for ubiquitin (known as FTLD-U) were found to contain TAR DNA-binding protein (TDP-43 protein), as did ALS cases, both sporadic and some familial. This group of patents is labelled as FTLD-TDP. TDP-43 is a 414 amino acid nuclear protein, encoded by TARDBP, a chromosome 1 gene. TDP-protein shuttles between the nucleus and the cytoplasm. In vitro, when its translocation to the nucleus is inhibited, TDP-43 accumulates, and is sequestered as cytoplasmic aggregates. Missense and nonsense mutations in TARDBP cause FTLD-ALS spectrum with a frequency of less than 1% in FTLD and around 1% in ALS. FTLD-TDP cases are further sub classified as: FTLD-TDP type A is most often associated with progranulin mutations. Pathological highlights are numerous short dystrophic neurites (DN), crescentic or oval neuronal cytoplasmic inclusions (NCI), concentrated primarily in neocortical layer 2. and moderate number of lentiform neuronal intranuclear inclusions (NII). Repeat expansion mutation in the C9orf72 gene is also associated with FTLD_TDP type A. FTLD-TDP43 type B is associated with FTD-ALS and bvFTD. Pathology also includes NCIs, but NIIs and DNs are rare. Males are more frequently affected and this group has the shortest life expect- ancy at just over five years on average. Hexanucleotide expansion mutation (GGGGCC) in the gene C9orf72 is associated with this sub type

24.17 Inherited neurodegenerative diseases 6237 FTLD-TDP43 type C features long DN in superficial cortical layers, predominantly in layer II, and clinically presents with SD (and occasionally bvFTD). At this time, there is no linkage to any gene. FTLD-TDP43 type D have few NCI and numerous NII and DN throughout all layers. This subtype is associated with valosin- containing protein (VCP) mutations, and is very rare at less than 1% of familial FTLD. Clinical presentation for type D is familial inclu- sion body myopathy with Paget Disease of Bone and frontotemporal dementia (IBMPFD). FUS Fused in sarcoma (FUS, also known as translocated in liposarcoma, TLS) codes for a 526 amino acid protein and is identified as a fu- sion oncogene causing human myxoid liposarcomas. The protein has several conserved domains, a transcriptional activation domain, multiple nucleic acid binding domains and a nuclear localization signal. It was. In the nucleus, FUS may be involved in regulation of transcription and pre-mRNA splicing. Mutations in the FUS gene are identified as a cause of fALS in 2009, representing around 4% of fALS. The FUS protein was found to be deposited in cytoplasmic inclusions in these patients. VCP Valosin-containing protein (VCP, also known as p97) is a conserved, multifunctional protein which comprises around 1% of total cellular protein and is a member of the class II AAA (ATPases associated with diverse cellular activities) family. It is known to paly diverse functions include ER and Golgi reassembly, nuclear envelope re- generation, proteolysis, spindle disassembly, chromosome conden- sation, DNA damage response, DNA replication, suppression of protein aggregation, autophagy, ER-associated protein degradation, and sex determination. VCP mutations are an underlying cause of IBMPFD (inclusion body myopathy with Paget’s disease of bone and frontotemporal de- mentia). Most individuals with IBMPFD present with myopathy, occurring in 80–90% of patients in adulthhood (c.44 years) with proximal and distal muscle weakness. Electromyography shows myopathic changes and biopsy shows myonuclear and sarcoplasmic inclusion bodies reactive with ubiquitin and TDP-43. A third of patients present with dementia a decade later with characteristic language

and/or behavioural dysfunction and FTLD-TDP D type pathology. C9orf72 The C9orf72 gene encodes a protein of unknown function, but pre- dicted function of the gene product based its structure, is to regu- late membrane traffic in conjunction with Rab-GTPase switches.
A hexanucleotide repeat mutation with the sequence GGGGCC in the first intron of C9orf72 was found to be the most common genetic cause of cause of fALS and FTD, responsible for around 40% of fALS and 21% of FTD. Normal copy number ranges from zero-30 copies to an excess of four thousand in mutation carriers. Pathologically, C9orf72 mutations are frequently categorized as FTLD_TDP43 type B pathology, however, have a type A pathology in the outer layers of the cerebral cortex is also described. The hexanucleotide repeat in the noncoding region of the C9orf72 gene allows expression of mutant proteins made of dipeptide repeats (DPRs) via an interesting phenomenon known as repeat-associated non-ATG dependent translation (RAN translation). RAN transla- tion occurs in the absence of the ATG codon and from both strands. In addition to the aberrant proteins themselves, a ‘toxic RNA’ hy- pothesis due to the propensity of the RNA of C9orf72 to form highly stable guanine quadruplexes (G-quadruplexes), and secondary structures formed from short tracts of G-rich sequence associating together is postulated. P62/sequestosome-1 p62, encoded for by the SQSTM1 gene, is a stress-inducible intracel- lular protein involved in the regulation of cell survival and death via regulation of cell signal transduction. Following the candidate gene approach identification of SQSTM1 mutation, it has been further re- ported in ALS and in FTLD. Ubiquilin 2 The UBQLN2 gene encodes ubiquilin-2 (UBQLN2), a member of the ubiquilin (UBQLN) family that regulates degradation of ubiqui- tinated proteins. Mutations in this gene have been found in very rare cases of dominantly inherited chromosome-X-linked ALS (X-ALS) and ALS with FTLD. Dementia with Lewy bodies Lewy body dementia (LBD) is distinguished by the presence of intracytoplasmic aggregates of α-synuclein and other proteins within neurons, especially the CA2/3 region of the hippocampus. LBD is a complex neurodegenerative disorder caused by the inter- action of genetic and environmental factors. Histologically, LBD is characterized by the presence of Lewy bodies, which are spherical intracytoplasmic deposits around the nucleus and along the den- drites of cortical and subcortical neurons. These inclusions, evident particularly in dopaminergic neurons, are mainly made up of fila- mentous α-synuclein and ubiquitin proteins. The disease is mostly sporadic; however, there are rare cases of familial aggregation. Missense mutations in the α-synuclein gene (SNCA) are demonstrated to be associated with the disease. Two different mutations (P123H and V70M) in two different families with LBD have been identified in the β-synuclein gene (SNCB). Clinically picture of LBD may be difficult to differentiate from Alzheimer’s disease or Parkinson’s disease with dementia. LBD is characterized by progressive cognitive impairment, wide ‘fluctu- ations’ in attention and alertness, recurrent visual hallucinations, and parkinsonis. Additional features LBD include: REM sleep be- haviour disorder, severe sensitivity to neuroleptics, repeated falls and syncope, transient loss of consciousness, delirium, and non- visual hallucinations. Prion disorders Prion diseases, or transmissible spongiform encephalopathies, are fatal neurodegenerative disorders that affect humans and animals. Prion diseases have in common the accumulation of an abnormal isoform of the normal human protein PrP. Prion diseases cause a spongiform change within brains associated with astrogliosis and neuronal loss. The key mechanism in the pathogenesis of prion dis- eases is the conversion of the cellular prion protein (PrPC) into PrPSc. Most cases are sporadic but 15% have a familial basis and 1% are acquired iatrogenic.

section 24 Neurological disorders 6238 PRNP is located on chromosome 20p12 in humans and codes for a 253 amino acid prion protein (PrP). To date, more than 30 muta- tions of PRNP found in

the open reading frame of this gene are the only cause of familial prion diseases, which include familial CJD, GSS, and fatal familial insomnia (FFI). Mutations are autosomal dominant point mutations and insertion/deletion mutations of octapeptide re- peats (OPRI/OPRD). A codon 129 polymorphism with homozygosity for methionine or valine results in greater susceptibility for sporadic or iatrogenic CJD, whereas heterozygosity at this codon is protective. Methionine homozygosity at this codon results in increased suscepti- bility to vCJD. FFI is associated with a mutation at codon 178 plus me- thionine on the polymorphic codon 129. If a valine residue is present at the polymorphic codon 129, CJD results rather than FFI. Amino acid substitutions at several other codons cause GSS. Creutzfeldt–Jakob disease (CJD) generally presents between ages 50 and 70 with dementia, myoclonus, and ataxia. It is rapidly pro- gressive with death usually within less than 1 year. The EEG of many of the patients contains 1- to 2-Hz triphasic periodic sharp waves. On MRI, hyperintensity is detectable on FLAIR and diffusion-weighted images in the neocortex, basal ganglia, thalamus, and cerebellum. A variant of CJD (vCJD), believed to be caused by transmission of bovine spongiform encephalopathy (BSE or ‘mad cow disease’) to humans, has been seen in young adults (average age 29 years). It presents with psychiatric symptoms, painful dysaesthesias, ataxia, dementia, and a movement disorder. The median survival is longer than in CJD (c.14.5 months). Diagnosis requires brain or tonsillar biopsy to demonstrate PrPSc. The pathology of vCJD is distinctive with diffuse vacuolization and PrP-containing plaques surrounded by a halo of the spongiform change. Another variant, Gerstmann–Sträussler–Scheinker syndrome (GSS), is an inherited form that occurs at an earlier age than CJD and progresses more slowly, with death resulting in 2–10 years. Signs include ataxia, decreased reflexes, and dementia. Amyotrophy and parkinsonian signs may also appear. EEG changes such as those in CJD are not present. Mild cerebral or cerebellar atrophy is present but there are fewer vacuolar changes than in CJD. There are extensive PrP-amyloid plaques and in some cases also neurofibrillary tangles. In FFI, the insomnia is untreatable but cognitive function is spared until late in the disease. Other signs are ataxia, pyramidal and extrapyramidal dysfunction, and dysautonomia. Pathological exam- ination reveals almost no vacuolization but neuronal loss and gliosis are found in the thalamus, inferior olives, and to a lesser degree in the cerebellum. Section V: Epilepsy genetics Genetic factors account for about 40% of the aetiological causes of epi- lepsy, but only about 1% are monogenic (Mendelian), being caused by mutation(s) in a single gene, and termed ‘genetic epilepsies’. The risk of epilepsy in the offspring and siblings of patients with epilepsy of any cause is 2–5%, with higher concordance in monozygotic compared to dizygotic twins. Genetic epilepsies may be ‘syndromic’, where epilepsy is a comorbid condition of another disorder or syndrome, or ‘non-syndromic’, where epilepsy is the core manifestations, and the latter are described in this section of this chapter. Genetic testing should be considered in any patient with epilepsy in whom there is a positive family history, or there are features such as developmental delay or abnormal neurologic examination that is not otherwise explained. Nonsyndromic genetic epilepsies Consideration of nonsyndromic genetic epilepsies can pragmatic- ally be based on age of onset of seizures. Epilepsies of neonatal onset Benign familial neonatal seizures (BFNS) This is an autosomal dominant syndrome characterized by multi- focal clonic or focal seizures, which typically begin on day 2 and spontaneously remit after a few weeks or months, recurring in later life in about 10% of cases. BFNS can be caused by mutations in the voltage-gated potassium channel genes KCNQ2 and KCNQ3, and some mutations of KCNQ2 are associated with severe epileptic en- cephalopathy, in which the use of retigabine (a potassium channel activator) is being investigated. Benign familial neonatal infantile seizures (BFNIS) This is an autosomal dominant syndrome that presents as afebrile, partial seizures with secondary generalization between day 2 and 7 months of age, with

spontaneous remission by 1 year. It is often caused by missense mutation of KCNQ2 (see Table 24.17.3). Neonatal epileptic encephalopathies These are severe neonatal and early infantile epilepsy syndromes in which recurrent clinical seizures are associated with impairment of cognitive, sensory and motor development (see Table 24.17.3). Mutations are often found in genes involved in a wide range of elements required for nerve function. Epilepsies of infantile onset Benign familial infantile seizures Benign familial infantile seizures is an autosomal dominant epi- lepsy with onset between 4 and 8 months of age. Seizures are par- tial, may cluster, with good response to treatment. Prognosis for remission is good. The syndrome is associated with multiple genes (Table 24.17.4). Dravet syndrome Dravet syndrome, also known as severe myoclonic epilepsy of in- fancy, was described first by Charlotte Dravet in 1978. In 2001, SCN1A gene mutations were found to be associated and more than 600 mutations have been described ever since. A website http://www.scn1a.info tracks new mutations. SCN1A encodes for the α-subunit of voltage-gated sodium channels which regu- late the excitability of neurons and neuronal networks. De novo truncations in SCN1A are found in 85% of Dravet syndrome pa- tients but missense mutations may also occur. Other SCN1A gene mutations have been implicated in generalized epilepsy with fe- brile seizures plus syndrome as well as other epilepsy syndromes. Severe loss-of-function mutations corroborate with severe epi- lepsy syndromes. Clinically infants present at the age of 6 months, typically with prolonged generalized febrile seizures with subsequent evolution into other seizure types such as myoclonic, complex partial seizures, atypical absence seizures. Cognitive and behavioural deterioration

24.17 Inherited neurodegenerative diseases 6239 Table 24.17.3 Genetics of nonsyndromic epilepsies of neonatal onset Epilepsy syndrome Epilepsy syndrome subgroup Inheritance Locus Gene Gene product Gene function BFNS BFNS AD 20q13.33 KCNQ2 Subunit voltage-gated K channel Subunit voltage-gated K channel activity AD 8q24.22 KCNQ3 Subunit voltage-gated K channel Subunit voltage-gated K channel activity BFNIS BFNIS AD 2q24.3 SCN2A α-subunit voltage-gated Na channel Subunit voltage-gated Na channel activity EIEE EIEE1 X-linked recessive Xp21.3 ARX Aristaless-related homeobox Homeobox transcription factor EIEE2 X-linked dominant Xp22.13 CDKL5 Cyclin-dependent kinase-like 5 Regulation of other gene function (MECP2) EIEE3 AR 11p15.5 SLC25A22 Solute carrier family 25, member 22 Mitochondrial carrier of l-glutamate EIEE4 AD 9q34.11 STXBP1 Syntaxin-binding protein 1 Synaptic vesicles docking and fusion EIEE5 AD 9q34.11 SPTAN1 Spectrin, α, nonerythrocytic 1 Regulation of receptor binding and actin cross-linking EIEE6/Dravet syndrome AD 2q24.3 SCN1A
SCN9A α-subunit voltage-gated Na channel Subunit voltage-gated Na channel activity AD 5q34 GABRG2 GABA-A receptor, γ-2 polypeptide GABA-A receptor activity EIEE7 AD 20q13.33 KCNQ2 Subunit voltage-gated K channel Subunit voltage-gated K channel activity EIEE8 X-linked recessive Xq11.1-q11.2 ARHGEF9 Rho guanine nucleotide exchange factor 9 Formation of postsynaptic glycine and GABA receptor clusters EIEE9 X-linked Xq22.1 PCDH19 Protocadherin 19 Cell signalling and adhesion EIEE10 AR 19q13.33 PNKP Polynucleotide kinase 3-prime phosphatase DNA repair EIEE11 AD 2q24.3 SCN2A α-subunit voltage-gated Na channel Subunit voltage-gated Na channel activity EIEE12 AR 20p12.3 PLCB1 Phospholipase C, β-1 Signal transduction EIEE13 AD 12q13.13 SCN8A α-subunit voltage-gated Na channel Subunit voltage-gated Na channel activity EIEE14 AD 9q34.3 KCNT1 (gain of function) Subunit voltage-gated K channel Subunit voltage-gated K channel activity EIEE15 AR 1p34.1 ST3GAL3 ST3 β-galacstoside α-2,3- sialyltransferase 3 Glycosylation of proteins EIEE16 AR 16p13.3 TBC1D24 Tre2-Bub2-Cdc16- domain family, member 24 Intracellular vesicular transport EIEE17 AD 16q12.2 GNAO1 Guanine nucleotide-binding protein, α-activating

polypeptide O gene Signal transduction EIEE18 AR 1p34.2 SZT2 Mouse seizure threshold 2 gene Induction of superoxide dismutase EIEE19 — 5q34 GABRA1 GABA receptor, α-1 GABA-A receptor function EIEE20 X-linked recessive Xp22.2 PIGA Phosphatidylinositol glycan, class A Anchoring proteins to cell surface EIEE 21 AR 12p13.31 NECAP1 NECAP Endocytosis-associated protein 1 Clarthrin-mediated endocystosis in synapses EIEE22 congenital disorder of glycosylation, type IIm X-linked dominant Xp11.23 SLC35A2 Solute carrier family 35, member 2 UDP-galactose transporter EIEE23 AR 1p31.3 DOCK7 Dedicator of cytokinesis 7 Guanine nucleotide exchange factor, role in neurogenesis EIEE24 AD 5p12 HCN1 Hyperpolarization-activated cyclic nucleotide-gated potassium channel 1 Function of this subset of K channels (continued)

section 24 Neurological disorders 6240 tends to correlate with the frequency of seizures. Treatment of Dravet syndrome is challenging. Some benefit may be seen with the use of stiripentol, topiramate, valproate, clobazam, clonazepam, and levetiracetam, as well as a ketogenic diet. Certain anticonvulsants including lamotrigine and carbamazepine may exacerbate seizures in these patients. In June 2018, the US FDA approved oral Cannabidiol [CBD] for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older. When compared with placebo, CBD was shown to be effective in reducing frequency of seizures in three randomized, double- blind, placebo-controlled clinical trials involving 516 patients with either Lennox-Gastaut syndrome or Dravet syndrome. West syndrome West syndrome is an infantile-onset severe epileptic encephalopathy syndrome. It is recognized by a triad of infantile spasms, developmental delay or regression, and a characteristic electroencephalographic pattern called hypsarrhythmia. Several early infantile epileptic encephalopathy syndromes progress into a West syndrome phenotype especially those with mutations in ARX and CDKL5 genes, del 1p36 and inv dup (15). Traditional medications are adrenocorticotrophic hormone and vigabatrin; often ketogenic diet, topiramate, felbamate, zomisamide, and valproate may help. Generalized epilepsy with febrile seizures plus Seizures often first occur in early childhood in association with fever but continue after the age of six in the absence of fever. Seizures may be tonic-clonic, myoclonic, atonic, or absence seizures, or even myoclonic-astatic epilepsy; vary rarely focal temporal lobe epilepsy has been described. In most children, neurological development is normal and the seizures present by age 11. Sodium channel genes, encoding the α1, β1, and α2 subunits have been implicated: SCN1A encoded on chromosome 2q24, SCN1B located on 19q13.1, and SCN2A, also mapped to chromosome 2q24, respectively. Mutations in the γ-aminobutyric acid (GABA) receptor γ-subunit gene, GABRG2, located on chromosome 5q34 have also been found in the generalized epilepsy with febrile seizures plus (GEFS+) phenotype (Table 24.17.4). Epilepsy of infancy with migrating focal seizures Epilepsy of infancy with migrating focal seizures, also known as malignant migrating partial epilepsies in infancy, is a rare syn- drome characterized by onset in the first six months of life of several refractory seizure types independently migrating from one cortical area to another. Mutations in KCNT1 and other genes are implicated (Table 24.17.4). KCNT1 encodes for a sodium-activated potassium channel highly expressed in neurons and cardiomyocytes. Mutations are typically gain-of-function mutations causing activation of the channel with pathologic potassium conductance. Although seizure frequency and severity typically improve with age, there remains severe degrees of developmental delay. Antiarrhythmic drugs like quinidine may provide a therapeutic target. Pyridoxine-dependent seizures The seizures in neonatal-onset epileptic encephalopathy are re- sistant to antiepileptic drugs but respond immediately to the administration of pyridoxine in greater than the normal physio- logical requirement. Plasma and urinary levels of

δ1-piperidine- 6-carboxylate (P6C) and α-aminoadipic semialdehyde (α-AASA) are increased due to mutations in ALDHTAI, the gene-encoding antiquitin, an α-AASA dehydrogenase. The accumulating P6C in- activates pyridoxal-5-phosphate, which is needed for GABA pro- duction, a central inhibitory neurotransmitter. Failure to recognize and treat this condition early can lead to permanent brain damage and lifelong intellectual impairment. Glucose transporter 1 deficiency syndrome Clinical manifestations of this infantile-onset disorder include se- vere seizures, intermittent ataxia, confusion, movement abnormal- ities, spasticity, sleep disturbances, and recurrent headaches. There is deceleration of head growth with acquired microcephaly, develop- mental delay, and cognitive impairments. Early appearance of epi- sodic eye movements simulating opsoclonus has led to work-up for an occult neuroblastoma. The absolute level of cerebrospinal fluid glucose is low and cere- brospinal fluid lactate concentration is also reduced. The disorder is due to new heterozygous mutations in GLUTI, which encodes a glucose transporter that is highly expressed in brain and red blood cells. The diagnosis may be confirmed by measuring the uptake of 3-O-methyl-d-glucose into erythrocytes. The seizures are refractory to conventional anticonvulsant medications and are exacerbated by phenobarbital, but respond to a ketogenic diet. Benign myoclonic epilepsy of infancy Benign myoclonic epilepsy of infancy starts in infancy with myo- clonic seizures, reflex myoclonus, and photosensitivity. The aetiology Epilepsy syndrome Epilepsy syndrome subgroup Inheritance Locus Gene Gene product Gene function EIEE25 AR 17p13.1 SLC13A5 Solute carrier family 13, member 5 Sodium-dependent citrate transporter SRGAP2- associated EIEE — 1q32.1 SRGAP2 Slit-Robo Rho GTP-ase activation protein 2 Neuronal migration and differentiation MEF2C-associated EIEE — 5q14.3 MEF2C MADs box transcription enhancer factor 2, polypeptide C Neuronal migration AD, autosomal dominant; AR, autosomal recessive; BFNIS, benign familial neonatal infantile seizures; BFNS, benign familial neonatal seizures; EIEE, early infantile epileptic encephalopathy; GABA, γ-aminobutyric acid; UDP, uridine-5-prime-diphosphate. Reprinted from Pediatric Clinics, Vol. 62, Hani AJ, Mikati HM and Mikati MA, Genetics of Pediatric Epilepsy, Pages 703–22, Copyright © 2015, with permission from Elsevier. Originally adapted from OMIM database. Available at: http://www.ncbi.nlm.nih.gov/omim/. Table 24.17.3 Continued

 is not known but 50% of patients have family history of epilepsy or febrile seizures. Familial infantile myoclonic epilepsy Familial infantile myoclonic epilepsy starts in early infancy with myoclonic seizures, febrile seizures, and tonic-clonic seizures; however, there is no psychomotor delay. Causative mutations are homozygous loss-of-function mutations in the TBC1D24, which regulates neurotransmitter release at the synaptic level (see Table 24.17.4). Epilepsies of childhood onset Early and late-onset childhood occipital epilepsy The early onset childhood occipital epilepsy, also known as Panayiotopoulos syndrome, with the hallmark of autonomic seiz- ures including vomiting and late-onset childhood occipital epilepsy (LOCOE) characterized by visual seizures are thought to be partly genetic given the increased incidence of epilepsy in first-degree members of patients. Benign epilepsy with centrotemporal spikes Benign epilepsy with centrotemporal spikes (BECTS) is the most common benign focal epilepsy of childhood.. Genome wide analysis showed linkage to a region on chromosome 11p13. Some cases have also been linked to GRIN2A mutations and to DEPDC5 mutations. Seizures, occurring between ages of 7 to 10 years, are unilateral sen- sorimotor involving face with speech arrest and hypersalivation. Childhood absence epilepsy In childhood absence epilepsy, although considered polygenic, mu- tations in genes encoding the various subunits of the GABA-A re- ceptor and mutations in the voltage-gated calcium channel subunits may contribute (Table 24.17.5). Seizures are marked by brief alter- ation of consciousness for an

average of 10 seconds followed by rapid return to baseline mental status within 2 to 3 seconds. Landau–Kleffner syndrome Landau–Kleffner syndrome (LKS) is a focal epilepsy with speech disorder with or without mental retardation. It is marked by epileptic Table 24.17.4 Genetics of nonsyndromic epilepsies of infantile onset Epilepsy syndrome Epilepsy syndrome Inheritance Locus Gene Gene name/Product Gene function BFIS BFIS1 AD 19q BFIS1 Benign familial infantile seizure 1 — BFIS2 AD 16p11.2 PRRT2 Proline-rich transmembrane protein 2 Transport of synaptic vesicles BFIS3 AD 2q24.3 SCN2A Sodium channel, voltage-gated type II, α-subunit Sodium channel activity BFIS4 AD? 1p36.12-p35.1 — — — Dravet Syndrome (EIEE6), SMEI Dravet syndrome AD 2q24.3 SCN1A SCN9A α-subunits of voltage-gated Na channel Subunit voltage-gated Na channel activity AD 5q34 GABRG2 GABA-A receptor, γ-2 polypeptide GABA-A receptor activity West syndrome Please refer to EIEE section in Table 24.17.3 Generalized epilepsy with febrile seizures plus GEFSP, type 1 (GEFSP1) AD 19q13.2 SCN1B β-subunits of voltage-gated Na channel Subunit voltage-gated Na channel activity GEFSP2, AD 2q24.3 SCN1A α-subunits of voltage-gated Na channel Subunit voltage-gated Na channel activity GEFSP3 AD 5q34 GABRG2 GABA-A receptor, γ-2 polypeptide GABA-A receptor activity GEFSP4 AD 2p24 — — — GEFSP5 AD 1p36.3 GABRD GABA receptor, δ-subunit GABA-A receptor activity GEFSP6 AD 8p23-p21 GEFSP7 AD 2q24.3 SCN9A α-subunits of voltage-gated Na channel Subunit voltage-gated Na channel activity GEFSP8 AD 6q16.3-q22.31 EIMFS Please refer to EIEE6, EIEE16, and EIEE14 in Table 24.17.3 for possible causative genes. EIMFS AR 11p15.5 SLC25A22 Solute carrier family 25, member 22 Mitochondrial carrier of l-glutamate EIMFS AR 20p12.3 PLCB1 Phospholipase C, β-1 Signal transduction Familial infantile myoclonic epilepsy FIME AR 16p13.3 TBC1D24 Tre2-Bub2-Cdc16- domain family, member 24 Intracellular vesicular transport BFIS, benign familial infantile seizures; EIEE, early infantile epileptic encephalopathy; EIMFS, Epilepsy of infancy with migrating focal seizures; SMEI, severe myoclonic epilepsy
of infancy. Reprinted from Pediatric Clinics, Vol. 62, Hani AJ, Mikati HM and Mikati MA, Genetics of Pediatric Epilepsy, Pages 703–22, Copyright © 2015, with permission from Elsevier. Originally adapted from OMIM database. Available at: http://www.ncbi.nlm.nih.gov/omim/.

section 24 Neurological disorders 6242 aphasia. LKS and some cases of BECTS may be caused by mutations of GRIN2A gene. Mutations lead to increase in open time and de- crease in the closed time of NMDA channels. Epileptic encephalopathy with continuous spike-and-wave during sleep This condition, caused by heterozygous mutations in the GRIN2A, manifests with seizures, cognitive regression, and electroencephalo graphic pattern of continuous spike wave during non-REM sleep. Epilepsies of adolescent onset Juvenile absence epilepsy This condition, which can be caused by mutations in several genes (Table 24.17.6), presents with absence seizures at about 12 years of age in association with generalized tonic-clonic seizures in most cases. Juvenile myoclonic epilepsy This condition, caused by mutations of the GABRA1, CACNB4, GABRD, EFHC1, and CLCN2 genes (see Table 24.17.3), presents with myoclonic jerks, generalized tonic-clonic seizures, and (sometimes) absence seizures. Autosomal dominant nocturnal frontal lobe epilepsy This condition is typically caused by mutations in genes encoding various nicotinic acetylcholine receptor subunits. Severe forms can be caused by mutations in the KCNT1 gene, which encodes a calcium-activated potassium channel. Autosomal dominant partial epilepsy with auditory
features (ADPEAF) This condition is caused by mutations of the LGI1 l(eucine-rich glioma-inactivated 1) gene in 50% of cases. Clinical presentation is with focal seizures and predominant auditory auras, commencing between the second and fourth decades. Epilepsies of variable age of onset Familial focal epilepsy with variable foci This autosomal dominant epilepsy may be cuased

by mutations in DEPDC5 (DEP domain-containing protein 5 involved in G-protein signalling pathways) gene. Clinical presentation is with daytime focal seizures, presenting before the age of 20 years, which arise from different foci in different family members (hence the name). Progressive myoclonic epilepsies (PME) These are mostly autosomal recessive disorders characterized by myoclonus, generalized tonic-clonic seizures, and progressive neurologic deterioration, with eventual development of cerebellar signs and dementia. Causes include neuronal ceroid lipofuscinoses, neuronopathic Gaucher's disease, the cherry red spot–myoclonus epilepsy syndrome (all lysosomal storage diseases); myoclonus Table 24.17.5 Genetics of nonsyndromic epilepsies of childhood onset Epilepsy syndrome Epilepsy syndrome Inheritance Locus Gene Gene product Gene function Early onset childhood occipital epilepsy Panayiatopoulos syndromea LOCOE LOCOE— described by Gastauta Benign epilepsy with centrotemporal spikes BECTS = Rolandic epilepsy AD 11p13 CAE CAE susceptibility gene 1 AD 8q24 CAE susceptibility gene 2 AD 5134 GABRG2 GABA-A receptor, γ-2 polypeptide GABA-A receptor activity CAE susceptibility gene 5 AD 15q12 GABRB3 GABA-A receptor, β-3 polypeptide GABA-A receptor activity CAE susceptibility gene 6 AD 16p13.3 CACNA1H α-1-subunit of voltage-gated calcium channel Voltage-gated Ca channel function CAE susceptibility gene 4 AD 5q34 GABRA1 GABA-A receptor, α-1 polypeptide GABA-A receptor activity LKS: subset of focal epilepsy with speech disorder LKS AD 16p13.2 GRIN2A Glutamate receptor, ionotropic, NMDA, subunit 2A Regulates NMDA receptor excitatory properties Epilepsy with myoclonic- atonic seizures Possible association with GEFSP 1, 2, and 3 (see Table 24.17.4) Lennox–Gastaut syndrome Please refer to EIEE genes in Table 24.17.3. Epileptic encephalopathy with continuous spike wave during sleep Please refer to LKS gene GRIN2A detailed above in this table BECTS, benign epilepsy with centrotemporal spikes; CAE, childhood absence epilepsy; LKS, Landau–Kleffner syndrome; LOCOE, late-onset childhood occipital epilepsy; NMDA, N-methyl-d-aspartate. a These syndromes are presumed to have a genetic aetiology, but no definite mutations have been identified. Reprinted from Pediatric Clinics, Vol. 62, Hani AJ, Mikati HM and Mikati MA, Genetics of Pediatric Epilepsy, Pages 703–22, Copyright © 2015, with permission from Elsevier. Originally adapted from OMIM database. Available at: http://www.ncbi.nlm.nih.gov/omim/.

epilepsy with ragged red fibres (a mitochondrial disorder); and two other conditions, Lafora body disease and Unverricht–Lundborg disease (Baltic myoclonus epilepsy syndrome). Familial PME can rarely be caused by mutations in other genes. Neuronal ceroid lipofuscinoses This class of hereditary neurodegenerative lysosomal storage diseases is a common cause of childhood-onset seizures with an es- timated incidence of 1 in 25 000. Common features are decline in cognition and motor functions, and blindness. Autofluorescent lipopigment accumulates within neurons and inclusion bodies char- acteristic of each variant can be seen by electron microscopy (EM). Infantile neuronal ceroid lipofuscinosis (CLN1) is characterized by blindness before age 2, seizures, and marked cerebral atrophy. The ultrastructural appearance of the stored substance is predominantly granular, osmiophilic, dense material. Late-infantile CLN2 patients present at age two to three with sleeplessness, seizures, and then visual loss. Curvilinear bodies are present on electron microscopy. The juvenile-onset patients (CLN3) develop retinal pigmentary de- generation in mid to late childhood and then seizures, and, as teens, cerebellar and extrapyramidal signs appear. On electron microscopy a pattern of fingerprint bodies predominates. Death in infantile NCL (CLN1) occurs in childhood whereas survival into adoles- cence or adult life is the norm for the other variants. See section on lysososmal storage disorders for further details about the neuronal ceroid lipofuscinoses. Neuronopathic Gaucher's disease Gaucher's disease is characterized by lysosomal storage of the glycosphingolipid,

glucocerebroside, within the reticuloendothelical system, involving principally the spleen, liver, and bone. It is due to deficiency of the hydrolytic enzyme, glucocerebroside β-glucosidase, encoded on chromosome 1; in the most common type 1 patient it rarely causes CNS complications. However, patients with the rare type 2 form fail to develop neurologically, become cachectic, with multiple brainstem signs and seizures. In the type 2 patient, death usually occurs before the age of two from pneumonia. Approximately 5% of patients with Gaucher's disease worldwide have, in addition to visceromegaly, slowly progressive neurological involvement which includes gaze initiation failure, strabismus, Table 24.17.6 Genetics of nonsyndromic epilepsies of adolescent onset Epilepsy syndrome Epilepsy syndrome Inheritance Locus Gene Gene product Gene function JAE JAE susceptibility gene 1 AD 6p12.2 EFHC1 EF-hand domain-containing protein 1 Enhances calcium influx JAE susceptibility gene 2 AD 3q27.1 CLCN2 Chloride channel 2 Regulates activity of the chloride channel JME JME susceptibility gene 1 AD 6p12.2 EFHC1 EF-hand domain-containing protein 1 Enhances calcium influx JME susceptibility gene 3 AR 6p21 JME susceptibility gene 4 AD 5q12-q14 JME susceptibility gene 5 AD 5q34 GABRA1 GABA-A receptor, α-1 polypeptide GABA-A receptor activity JME susceptibility gene 6 AD 2q23.3 CACNB4 Voltage-gated Ca channel, β-4 subunit Voltage-gated Ca channel activity JME susceptibility gene 7 AD 1p36.33 GABRD GABA receptor, δ-subunit GABA-A receptor activity JME susceptibility gene 8 AD 3q27.1 CLCN2 Chloride channel 2 Regulates activity of the chloride channel JME susceptibility gene 9 AD 2q33-q36 ADNFLE ADNFLE 1 AD 20q13.33 CHRNA4 α-4 subunit of nAch receptor Regulates nAch receptor GABAergic inhibition ADNFLE 2 AD 15q24 ADNFLE 3 AD 1q21.3 CHRNB2 β-2 nAch receptor Regulates nAch receptor GABAergic inhibition ADNFLE 4 AD 8p21.2 CHRNA2 α-2 subunit of nAch receptor Regulates nAch receptor GABAergic inhibition ADNFLE 5 AD 9q34.3 KCNT1 subunit voltage-gated K channel Subunit voltage-gated K channel activity Autosomal dominant partial epilepsy with auditory features Also known as AD lateral temporal lobe epilepsy AD 10q23.33 LGI1 Leucine-rich, glioma-inactivated protein Regulates glutamatergic synapse development Ach, acetylcholine; AD, autosomal dominant; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; Ca, calcium; GABA, γ-aminobutyric acid; JAE, juvenile absence epilepsy; JME, Juvenile myoclonic epilepsy; Na, sodium; nAch, nicotinic acetylcholine. Reprinted from Pediatric Clinics, Vol. 62, Hani AJ, Mikati HM and Mikati MA, Genetics of Pediatric Epilepsy, Pages 703–22, Copyright © 2015, with permission from Elsevier. Originally adapted from OMIM database. Available at: http://www.ncbi.nlm.nih.gov/omim/.

section 24 Neurological disorders 6244 developmental delay, and, in a few patients, cardiac symptoms. Some develop myoclonic seizures, which progress in frequency and severity and become unresponsive to anticonvulsant therapy. Diagnosis of this autosomal recessive disease can be made by assay of blood β-glucosidase activity. Enzyme replacement therapy is effective in correcting the haematological abnormalities (anaemia, thrombocytopenia), and promotes reduction in the size of the liver and spleen but has proved ineffective in halting the progression of the myoclonic encephalopathy. Cherry red spot–myoclonus epilepsy syndrome (sialidosis type 1) This autosomal recessive lysosomal storage disease begins in late childhood or early adolescence with action myoclonus. Subsequently, generalized seizures and polymyoclonus develop. A cherry red spot may be seen in the macula early in the course of the disease, with blindness ensuing before significant cognitive de- cline occurs. Eventually the patient becomes bedridden and totally disabled by multiple myoclonic jerks. Vacuolated lymphocytes are present in peripheral blood and foamy histiocytes may be found in the bone marrow. Within urine, there is a marked increased in sialic acid-containing oligosaccharides. The disorder is due to a deficiency of lysosomal α-

neuraminidase located on chromosome 6p21.3. Myoclonic epilepsy with ragged red fibres Patients with MERFF present in early adult life with short stature, myoclonus, seizures, ataxia, muscle weakness, and sensory neur- opathy. Subsequently, dementia, hearing loss, and optic atrophy occur. This is a lactic acidosis and ragged red fibres are seen on a muscle biopsy with Gomori's trichrome stain. The principal neuro- pathological findings are degeneration of the dentate nuclei and superior cerebellar peduncles, the spinocerebellar tracts, and the posterior columns of the spinal cord. The cause in most cases is a point mutation at position 8,344 of the mitochondrial gene for tRNALys. Lafora's body disease This autosomal recessive disease begins in late childhood or early adolescence and progresses to death within 5 years. Most patients have a mutation in the EPM2A gene located on chromosome 6q23– 25 coding for the protein laforin. A few patients have a mutation in EPM2B instead which codes for malin. Tonic-clonic and myoclonic seizures, polymyoclonus, and pro- gressive mental deterioration occur. Cerebellar ataxia, optic atrophy, rigidity, and exaggerated reflexes develop later. On MRI there is moderate cerebellar atrophy and intracellular inclusion bodies com- posed of polyglucosan are present within neurons of the cerebral cortex, cerebellar dentate nuclei, liver, muscle, and axillary sweat glands. The last is a preferred site for a diagnostic biopsy. Unverricht–Lundberg disease (Baltic myoclonus) This autosomal recessive progressive encephalopathy is particularly frequent in Finland and Estonia, hence the term 'Baltic myoclonus'. This disorder is caused by a sequence alteration in the cystatin B gene (CSTB) on chromosome 21, which involves expansion of a dodecamer (CCCCGCCCCGCG) in the 5-′flanking area of CSTB. A few patients with point mutations have also been described. Onset is in childhood or adolescence and begins with generalized seizures. They are more frequent on awakening. Various stimuli will intensify the polymyoclonic activity. Cerebellar ataxia, dysarthria, pyramidal signs, distal muscle wasting, and over time mental de- terioration become evident. Nerve cell loss occurs in the cerebellar cortex, dentate nuclei, and thalami, and sometimes also in the basal ganglia, brainstem, and anterior horn cells of the spinal cord. Some patients have benefited from 5-hydroxytryptophan, piracetam, or baclofen, but the condition may be worsened by phenytoin, which should be avoided. Syndromic genetic epilepsies Syndromic genetic epilepsies include disorders where epilepsy is part of a constellation of symptoms that determine the clinical phenotype. Table 24.17.7 summarizes some common syndromic epilepsy syndromes. Rett Syndrome De novo sporadic cases of X-linked dominant Rett syndrome are more common (>99%) than familial cases (<1%); both caused in 9% of cases by loss-of-function mutations in the gene-encoding methyl-CpG-binding protein 2 (MECP2) at Xq28. MeCP2 is widely expressed in many organs, and its highest expression is detected in brain, lung, and spleen. MeCP2 is a multifunctional protein that is involved in transcriptional regulation as well as modulating chro- matin structure. Mutations in the genes cyclin-dependent kinase- like 5 and forkhead box protein G1 have been reported to cause Table 24.17.7 Genetics of some syndromic epilepsies Syndrome Genes Mode of inheritance Clinical features Rett syndrome MECP2 X-linked dominant Ataxia, postnatal microcephaly, severe neurodevelopmental problems, especially with movement and absent or deficient speech, regression and breathing abnormalities Angelman syndrome UBE3A Uniparental disomy, maternal deletion Severe cognitive disability, absent speech, periods of inappropriate laughter, postnatal microcephaly, ataxic gait, jerky movements, and epilepsy Tuberous sclerosis TSC1
TSC2 Autosomal dominant Skin (i.e. hypomelanotic macules, facial angiofibromas, shagreen patches, fibrous facial plaques, ungual fibromas), central nervous system (i.e. cortical tubers, subependymal nodules, subependymal giant cell astrocytoma), kidney (i.e. angiomyolipomas, cysts), and heart (i.e. rhabdomyomas, arrhythmias) Mowat–Wilson syndrome ZEB2 Autosomal

dominant Microcephaly, agenesis of the corpus callosum, cognitive disability with severe speech impairment, and seizures Pitt–Hopkins syndrome MBD5
TCF4 Autosomal dominant Intellectual disability with severe speech impairment, motor incoordination, postnatal microcephaly, breathing anomalies, and seizures Data from Noh GJ, Jane Tavyev Asher Y, Graham JM Jr. Clinical review of genetic epileptic encephalopathies. Eur J Med Genet 2012; 55(5):281–98.

24.17 Inherited neurodegenerative diseases 6245 atypical, variant, or congenital Rett syndrome. Reett syndrome oc- curs with a frequency of 1 in 10 000–20 000 girls with no proclivity for a particular race or ethnic group. Dr Andreas Rett first described Rett syndrome in 22 girls with a progressive neurologic syndrome with seizures. Rett syndrome is characterized by early normal growth and development for at least six months of age with subsequent regression. Some early signs may be evident by 2–4 months of age such as hypotonia, jerkiness in limb movement, and deceleration of head growth, before recognition of developmental regression. Arrested cognitive and motor develop- ment, loss of acquired verbal skills and stereotyped repetitive hand movements with loss of normal hand function occur beginning around 12–18 months of age. This onset of this nascent develop- mental regression may be abrupt over a span of weeks to months associated with severe sleep disturbances, irritability, and poor eye contact that is occasionally mistaken for autism. A more indolent course of neurologic deterioration ensues often ending in significant motor disability and a wheel chair bound state. The disease even- tually reaches a plateau and patients may survive into their sixth or seventh decade. Four stages are identified following a normal pre- natal and postnatal development of about 5 months. Stage I is her- alded by an early onset of developmental stagnation at 6 months to 1.5 years of age. During this period, major RTT phenotypes such as microcephaly (reduced brain/head size), reduced growth rate, loss of language and behavioural skills, and seizures start to appear. Stage II is mainly defined by rapid developmental regression with an onset of 1–4 years of age. There is loss of already acquired skills in commu- nication and behaviour and show symptoms of mental retardation. Stage III is usually referred to as pseudo-stationary or plateau period that lasts 4–7 years following stage II, also referred to as wake-up period because some patients are able to regain certain skills such as communication abilities. Nonetheless, there is progression of the re- spiratory problems, disturbed sleeping patterns, scoliosis (abnormal curvature of the spine), anxiety and hand apraxia/dyspraxia. Stage IV marks later motor deterioration during which patients lose their ability to walk and become nonambulatory. In more severe cases, patients may develop parkinsonian phenotype. The last stage may last from several years to decades. Epilepsy is very common in Rett syndrome with frequency ran- ging from approximately 50%-90%; the course and severity of epi- lepsy is often variable. Most seizures appear between 2 to 5 years of age (median onset is 4 years), usually at clinical stages II-III. Non- MECP2 mutations are more likely in patients with onset of seizures prior to one year of age. Although not established, it is suggested that early onset of seizures may be associated with more seizure types, more intractable epilepsy, and status epilepticus. All seizure types may be present in Rett syndrome including complex partial, gen- eralized tonic-clonic, tonic, and myoclonic seizures, with absence and clonic seizures being less frequent. The severity of epilepsy often tends to decline after adolescence even in intractable cases. Myriad of other behaviours seen in Rett syndrome patients may be misidentified as seizures by parent including hand stereotypies, breath-holding, and cyanosis, hyperventilation, staring, unusual eye movements (oculogyric movements, blinking episodes), oral fa- cial dyskinesias, unwarranted bouts of laughing or screaming, and motor abnormalities (tremor, dystonia, jerking, spasticity, and epi- sodic atonia).

Chaotic breathing patterns in the waking state, but not during sleep, are common. EEG patterns can also be classified into four stages that parallel the clinical stages. At stage I EEG results tend to be normal. At stage II (18 months- 3 years) slow background activity is characteristic- ally seen during wakefulness. Rolandic spikes (focal spikes in the centrotemporal regions) may be seen as the first EEG abnormality, often continuing into stage III. With clinical progression, poorly de- veloped or absent sleep spindles with augmentation of epileptiform activity may be seen. During stage III (plateau 2–10 years) seizure burden is prominent, sleep patterns continue to be abnormal and waking background activity remains slowed. During this period a unique pattern of bilaterally synchronous bursts of pseudo-periodic δ activity and generalized rhythmic spike discharges are seen most prominently during sleep. In stage IV (late motor deterioration) slowing of the background activity is persistent epileptiform abnor- malities on EEG; however, clinical seizures are generally no longer a prominent feature. Choice of the ideal first anticonvulsant drug remains unclear. Moreover with up to 50% are intractable and require polytherapy for seizure control. Common drugs reported in clinical practice as first- or second-line monotherapy for Rett syndrome include val- proate and lamotrigine. Medications like valproate, lamotrigine, and Topamax may address other behavioural comorbidities of Rett syn- drome such screaming episodes or mood stability. The consensus statement by the International Ketogenic Diet Study Group lists Rett syndrome as a condition in which the ketogenic diet has been reported as ‘probably’ particularly beneficial. Many children with Rett syndrome are fed with gastrostomy tubes, so they can be easily started on the ketogenic diet without compliance issues. Vagus nerve stimulation has demonstrated 50% reduction in seizure frequency in small patient series. Epileptic encephalopathy due to other inborn errors of metabolism Numerous hereditary metabolic encephalopathies other than those described earlier are associated with seizures. In the neonatal period and early infancy these include disorders of amino acids and or- ganic acids, urea cycle disorders, biotinidase deficiency, peroxi- somal and mitochondrial diseases, sulphite oxidase deficiency, and 3-phosphoglycerate dehydrogenase deficiency. Seizures presenting in the late-infantile and early childhood period may indicate a lyso- somal disorder, GABA transaminase deficiency, or creatine synthase deficiency. Disorders to consider when seizures present in later childhood or adolescence include, in addition to those listed earlier, acute intermittent porphyria and early onset Huntington’s disease. In all cases in which the diagnosis is obscure, routine work-up should include a metabolic screen of blood and urine, plasma amino acids, total, free, and acylcarnitines, urine organic acids, brain CT or MRI, very-long-chain fatty acids for peroxisomal disease, blood lac- tate and pyruvate for mitochondrial disorders, and skin biopsy for electron microscopy to rule out a lysosomal disease. Alpers’ syndrome Progressive encephalopathy with intractable seizures, diffuse neur- onal degeneration, and cortical spongiosis with and without liver disease are features of Alpers’ disease. It usually affects infants and young children, but rare juvenile cases are also known. Development delay may precede the onset of seizures, which may start abruptly and consist of various types in individual patients including a

 marked myoclonic component. Marked motor retardation and in- tellectual impairment with blindness ensue. Liver dysfunction with jaundice and hepatomegaly may develop. CT and MRI show pro- gressive cerebral atrophy. Mutations in the gene coding for the cata- lytic subunit of the mitochondrial DNA (mtDNA) polymerase γ (POLGI) have been found in a wide phenotypic spectrum of patients with this autosomal recessive disease. Menkes’ kinky hair disease The disease is caused by mutations in the ATP7A (MNK) gene en- coded on chromosome Xq13.3. This X-linked disorder of copper transport causes profound neurological deterioration with the early onset of seizures, abnormal face and hair, hypothermia, skeletal

abnormalities, and arterial degeneration. The scalp hair is sparse, stubby, and greyish in colour. Under a microscope, the hairs are seen to be twisted and display partial breaks. Seizures including myo- clonic jerks are almost constant and survival is generally less than 2 years. Serum copper and ceruloplasmin levels are very low, and brain copper is reduced due to poor absorption of copper from the intestine. Section VI: Headache Disorders In the current classification of headache disorders, headache at- tributable to genetic disorders is not classified separately. Genetic disorders that include headache as their primary, or one of their primary, manifestation are included in International Headache Classification-II as secondary headaches included under 'Headache attributed to cranial or cervical vascular disorder'. The classification thus implies that a vascular pathology causes headache in these gen- etic disorders. Migraine is one of the prominent presenting features of several genetic cerebral small vessel diseases, which include cere- bral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL); retinal vasculopathy with cere- bral leukodystrophy (RVCL); and hereditary infantile hemiparesis, retinal arteriolar tortuosity, and leukoencephalopahty. The mech- anisms underlying the development of headache in these genetic vasculopathies are not yet well understood. CADASIL CADASIL is the most common autosomal dominant nonamyloid, noninflammatory adult-onset small vessel arteriopathy affecting the small-sized arterioles. It is genetically caused by mutations in NOTCH3 located on chromosome 19p13.2-p13.1. NOTCH3 protein is a heterodimeric receptor with an extracellular, ligand- binding domain, a transmembrane domain, and a cystoplastmic domain. The NOTCH3 gene belongs to the evolutionary conserved Notch receptors family and encodes a 2,321-amino-acid-long single pass transmembrane protein, a cell surface receptor that, in human adult tissue, is solely expressed on vascular smooth muscle cells. The protein participates in signal transduction pathway, crit- ical for vascular development, homeostasis, and vascular smooth muscle cells (VSMC) differentiation and maintenance. Of the 33 exons, pathogenic missense mutations occur in exons 2–24 in over 95% of cases. The exons encode the epidermal growth factor- like repeats (EGFR), each of the repeat has six cysteine residues. Invariably, mutations lead to an addition or deletion of cysteine, leaving behind an odd number of cysteine residues within a given EGFR. Histopathologically, there are diffuse lesions of the hemispheric deep white matter and multiple lacunar infarcts in the white and deep grey matter, as well as in the brain stem. Small arteries and arterioles show loss of smooth muscle cells, prominent thickening of the wall, and deposition of uncharacterized granular osmiophilic material (GOM), located extracellularly and close to the cell sur- face of smooth muscle cells and pericytes. Eventually, there is de- generation and disappearance of VSMCs. In addition, there is an abnormal accumulation of the extracellular domain of NOTCH3 protein (NOTCH3ECD) at the plasma membrane of vascular smooth muscle cells and brain pericytes in close vicinity to, and within, GOM deposits. A small study from Scotland provided an estimate of 4.15 cases/ 100 000; however, the precise prevalence of CADASIL is unknown. CADASIL is characterized by four cardinal manifestations: (1) mi- graine with aura (MA) in 30–40% of patients, with an average age of onset of 30 years; (2) ischaemic events in 60–85% of patients, with an average age of first event of 49 years; (3) mood disturbances in 20% of patients; and (4) cognitive decline after the age of 50 years and dementia by the sixth to seventh decade of life. The cognitive deficit is mostly executive dysfunction and change in personality. Average age at diagnosis of CADASIL is between 40 and 50 years. Atypical migraine has been described in up to 50% of cases with prolonged aura, hemiplegia, or basilar migraine. Brain imaging in CADASIL highlights the leukoaraiosis seen as assymmetric areas of increased signal on T2-weighted MRI located in deep and periven- tricular white matter. The white matter intensities may be. Lacunar infarcts, subcortical lacunar lesions, and microbleeds are seen on imaging later in life. CARASIL Although migraine is not a feature of CARASIL, it is included here for sake of organizational

convenience. Analogous to CADASIL, CARASIL as implied by the name, an autosomal recessively dis- order. The gene defect is in a serine peptidase, HTRA1. HTRA1 belongs to the family of high-temperature requirement A serine proteases, which participates cell signalling and protein degradation (Fig. 24.17.17). The clinical features of CARASIL are in many respects similar to those in CADASIL. Half of the patients experience recurrent ischaemic lacunar strokes. There is a stepwise, progressive impair- ment of brain function leading to dementia, usually by the age of 30 to 40 years. Premature diffuse baldness is common especially in males. 80% of the patients suffer from disc herniation and degen- erative spondylosis at lower thoracic or upper lumbar levels causing back pain. Brain imaging is similar to CADASIL. Retinal vasculopathy with cerebral leukodystrophy RVCL was originally described in three families under three dif- ferent disease names: cerebroretinal vasculopathy (CRV), hereditary vascular retinopathy, and hereditary endotheliopathy, retinopathy, nephropathy, and stroke. Their allelic nature was established fol-lowing discovery of the disease-causing gene, which encodes the 3′-5′exonuclease TREX1. Being 3′-5′exonuclease, it may play a role DNA editing and repair. Trex1 protein is part of the SET complex, which is involved in apoptosis induced by cytoxic T-cells and killer

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