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24.10.2 Demyelinating disorders of the central nervous system Alasdair Coles and Siddharthan Chandran ESSENTIALS The common feature of all of the demyelinating diseases is that, ini- tially at least, the oligodendrocyte-myelin unit is the primary target, with the axon comparatively spared. There are a range of causes, both acquired and inherited. Multiple sclerosis is the commonest and protoypic condition. Pathophysiology—demyelination is followed by predictable elec- trophysiological consequences including impaired conduction and over time progressive neuronal injury with variable re-myelination. Multiple sclerosis Epidemiology—a disease of northern Europeans, occurring less fre- quently in other racial groups. The leading causing of acquired adult neurological disability in many industrialized nations. Pathology—characterized histologically by breakdown of the blood–brain barrier and multifocal inflammatory-mediated de- myelination leading to ‘plaques’ throughout the central nervous system. Neurodegeneration is prominent in the later stages of disease. Aetiology—unknown, but involves interplay between genes (fa- milial recurrence rate 15%, modest increase in risk from many genes) and the environment (possible effects from vitamin D status, smoking, and viral infection in childhood or adolescence). Clinical features—fatigue is common. Acute demyelinating optic neuritis is a first manifestation in up to 20% of patients. Impaired mo- bility affects most patients, usually as a result of spinal cord disease. Altered sensation is almost universal, autonomic symptoms occur in most, and cerebellar involvement is common. Abnormalities of eye movement are frequent, including ‘internuclear ophthalmoplegia’, a sign that is nearly always due to multiple sclerosis. Cognitive impair- ment occurs in up to 65% of patients. Clinical course—variable and unpredictable. Most patients ex- perience a relapsing and remitting course, characterized over time by three phases—relapse with full recovery, relapse with persistent deficits, and secondary progression. Diagnosis—multiple sclerosis can reliably be diagnosed using clinical criteria and without laboratory support. There is no single diagnostic laboratory investigation, but the most useful investiga- tions are (1) MRI demonstrating lesions disseminated in time and/ or space; (2) cerebrospinal fluid analysis revealing oligoclonal im- munoglobulin bands; (3) electrophysiology showing demyelination in central pathways. Management—the complex and progressive nature of disability requires a multidisciplinary approach. Symptomatic manage- ment may be required, for example, for bladder symptoms, con- stipation, or spasticity. Corticosteroids are effective in reducing the duration of acute demyelinating episodes but have no impact on the eventual degree of recovery or the subsequent disease course. Disease-modifying treatments are effective only in the inflamma- tory relapse-remitting phase of disease and include β-interferons, glatiramer acetate, fingolimod, and the humanized monoclonal antibodies natalizumab and alemtuzumab. There is not yet a con- sensus on how early and how aggressively multiple sclerosis should be treated.
Introduction: demyelinating disorders as potentially treatable conditions A distinguishing feature of vertebrate development is the forma- tion of compact myelin around axons, produced by oligodendro- cytes in the central nervous system and Schwann cells in the peripheral nervous system. This insulating material reduces the escape of current across the axon and allows for passive propa- gation of the action potential down myelinated segments of the nerve until it arrives at a break in the myelin, at a node of Ranvier, where a new action potential is actively triggered. The advantage of this ‘saltatory’ conduction is speed, and greater efficiency of energy and space. Myelinated nerves conduct the action potential more rapidly than in unmyelinated fibres. In demyelinating disorders of

24.10.2 Demyelinating disorders of the central nervous system 6027 the central nervous system, the oligodendrocyte-myelin unit is the primary target of pathology and conduction of the nerve impulse first slows and then fails. Multiple sclerosis, the prototypic demyelinating disorder of the central nervous system, is the leading causing of neurological dis- ability among young adults in many industrialized nations. In the last two decades therapies have been licensed with increasing cap- acity to suppress the inflammation which underlies the condition, leading to durable benefits to patients. The next most prevalent demyelinating disease is neuromyelitis optica. Originally thought to be a variant of multiple sclerosis, it is now recognized to be a distinct disease whose treatment is radically different from mul- tiple sclerosis. The common feature of all of the demyelinating diseases (listed in Table 24.10.2.1) is that, initially at least, the axon is compara- tively spared with the dominant pathology being inflammatory- mediated damage to the oligodendrocyte-myelin unit. This means that anatomical connections are not disrupted, which makes the task of functional repair considerably easier than in disorders which destroy neuronal pathways. Treatments to promote remyelination are currently under investigation in multiple sclerosis and the leukodystrophies. In some demyelinating disorders, most notably multiple scler- osis, there is a later phase of progressive disability which is due to neuronal loss. These observations raise questions about the de- pendence of neuronal integrity on myelin and glial support. The predominant strategies to prevent the neurodegeneration of mul- tiple sclerosis are early treatment to prevent demyelination along with, conceivably in the future, combinatorial neuroprotective treatments such as remyelination therapy to restore the glial-axon relationships. Neurobiology of demyelination and remyelination Origin of oligodendrocytes Oligodendrocytes synthesize and maintain the compact myelin that ensheathes axons. Oligodendrocytes, in contrast to neurons, are pre- dominantly specified postnatally and continue to divide and migrate as oligodendrocyte precursor cells (OPCs). Identification of the Olig genes has significantly advanced understanding of the molecular regu- lation of developmental and adult oligodendrogenesis. In addition to its established role in specifying neurons and OPCs in the developing CNS, emerging evidence implicates Olig in self-renewal of neural stem cells and adult oligodendrogenesis in the normal and injured brain. These findings—together with accumulated insights into the prolif- erative, migratory, and survival requirements of OPCs—have resulted in the oligodendrocyte lineage being the best characterized of all cells of the central nervous system. The application of that knowledge may in time lead to the development of potential neuroprotective thera- peutic targets in the context of demyelinating disease. Myelination Myelination occurs when the membranous processes of mature oligodendrocytes contact and wrap serially around axons. The result is compaction of myelin sheaths at two points of apposition, apparent on ultrastructural analysis as major and minor dense lines. Myelin is predominantly composed of lipids (70–80% dry weight; cholesterol, phospholipid, and galactolipids) and protein (20–30% dry weight). The major myelin-specific lipid galactocerebroside can be used to identify myelinating glia. The major proteins are proteolipid protein, myelin basic protein, and the myelin-specific enzyme 2’,3’-Cyclic-nucleotide 3’-phosphodiesterase. Table 24.10.2.1 Classification of demyelinating disorders of the central nervous system Disease Features Acquired Inflammatory Multiple sclerosis Very common: starts with relapsing-remitting episodes of e.g. optic nerve, spinal cord, and brainstem demyelination; later secondary progressive disease Neuromyelitis optica spectrum disorder Common: combinations of longitudinally extensive myelopathy, area postrema, and optic nerve lesions; due to anti-aquaporin 4 antibodies Acute disseminated encephalomyelitis Common: postinfectious, extensive cortical and brainstem demyelination Longitudinally extensive myelitis Common: postinfectious, or as part of NMO spectrum disorder Relapsing optic neuritis

Rare: some associated with anti-MOG antibodies and others dependent on corticosteroids Balo’s concentric sclerosis Rare: rings of demyelination and unaffected tissue causing lobar syndromes Harding’s disease Rare MS-like disease in people with Leber’s mitochondrial mutations Noninflammatory Central pontine myelinolysis Common: occurs with rapid correction of hyponatraemia Toxic disseminated encephalomyelitis Rare: due to inhaled vapour of opiates and cocaine Inherited Adrenoleukodystrophy Rare: in adults causes myelopathy, neuropathy, and adrenal failure Metachromatic leukodystrophy Rare: causes progressive epilepsy, neuropathy, and cognitive impairment Pelizaeus–Merzbacher disease Very rare: eye movement disorders, cognitive impairment, and neuropathy; due to proteolipid protein gene mutations Krabbe’s disease Very rare: epilepsy, cognitive impairment, and neuropathy; due to deficiency of α-galactocerebrosidase Autosomal-dominant adult leukodystrophies Very rare as adult

section 24 Neurological disorders 6028 Each high resistance myelin segment is separated by the unmyelin ated high conductance node of Ranvier. This specialized struc- ture, characterized by clusters of voltage-gated sodium channels, is the site of active generation of the action potential. Myelinated internodal segments contain dispersed sodium channels at a much lower density insufficient to support conduction. Pathophysiology of demyelination Demyelination is followed by predictable electrophysiological con- sequences including impaired saltatory conduction, decreased con- duction velocity, and variable degrees of conduction block. The extent to which these changes cause symptoms is less predictable and depends upon the redundancy within the pathway affected and the capacity of the nervous system to circumvent the lost func- tion. There are several mechanisms of symptom recovery early in the course of multiple sclerosis. Plastic functional reorganization of the nervous system may circumvent the disrupted pathway. An adaptation of the axon to demyelination is that sodium channels are expressed in demyelinated patches of axon membrane. This can re- store active conduction. But it may also be maladaptive; the ensuing increase in intracellular sodium concentration requires greater ac- tivity of the sodium-potassium exchanger. Especially when nerve firing is rapid, the metabolic strain of extruding sodium may cause axonal degeneration. As with many disorders of the nervous system, the clinical symp- toms and signs may be negative (loss of function), or positive (spon- taneous, involuntary, and paroxysmal). Either category can prove equally disabling. But there are features specific to demyelination, not seen in axonal loss. For instance, electrophysiological tests of optic tract function (‘visual evoked potentials’) will often show slowing of conduction following inflammatory demyelination in the optic nerve. Similar slowing may also be seen in brainstem and somatosensory evoked potentials after demyelination of the relevant pathways. In partially demyelinated axons, the action potential may propa- gate normally but can break down more easily to external chal- lenges. The best example is the ‘Uhthoff phenomenon’: symptoms occur on exercise or heating (e.g. in a hot bath) and disappear on cooling. As myelin is heated, so its insulating capacity reduces; cur- rent escapes from the axon, fails to trigger a new action potential at the node of Ranvier and so conduction fails. Also, the partially demyelinated nerve may discharge with mechanical stretching. Typical movement-induced symptoms including flashes of light on eye movement, and the electric sensation that spreads down the spine, limbs, or anterior chest wall after neck flexion—Lhermitte’s symptom and sign. Ephaptic transmission occurs between neigh- bouring and partially demyelinated axons giving rise to paroxysmal symptoms of demyelination usually manifesting as trigeminal neur- algia, ataxia, and dysarthria, or tonic brainstem seizures. These are often triggered by touch or movement. Remyelination Endogenous remyelination may restore function in demyelinating disease. In multiple sclerosis, it has long been

known that acute lesions frequently show an increase in the number of oligo- dendrocyte precursors and may undergo remyelination, evident as shadow plaques. Remyelination, found at all stages of disease, is histologically identified by inappropriately thin myelin lamellae, with a short internode, and widened nodes of Ranvier. The finding that remyelination is associated with less axonal injury compared with inactive demyelinated plaques, suggests that remyelination is neuroprotective. The source of remyelinating cells is presumed to be the oligodendrocyte progenitor, which is found in the lesions of multiple sclerosis, although recent evidence also suggests a role for adult subventricular zone derived stem cells. It is clear that remyelination is not sufficient to prevent disability in most cases of multiple sclerosis. This may be because the waves of inflammation overwhelm endogenous capacity for repair, or that there is a pri- mary failure of remyelination, perhaps increasing with age. Multiple scler osis Pathology The most common demyelinating disorder is multiple sclerosis, characterized histologically by breakdown of the blood–brain bar- rier and the development of multifocal foci of inflammation in the brain and cord, called ‘plaques’. In all but the most severe forms, perivascular inflammation evolves through stages of acute axonal injury, demyelination, oligodendrocyte depletion, remyelination, astrocytosis and chronic neurodegeneration (Fig. 24.10.2.1). The order and relationship of these separate components is still de- bated, but the consensus based on a wealth of evidence is that mul- tiple sclerosis is primarily an inflammatory disease with secondary neurodegeneration. Plaques are widely distributed, but concen- trated around venous networks, the ventricles, and in the corpus callosum, optic nerves, brainstem, and cervical cord. A simplified scheme is that multiple sclerosis starts with inappro- priate activation of a peripheral T cell directed against a myelin antigen. This T cell then proliferates, crosses the intact blood-brain- barrier, and enters the central nervous system. There it encounters its antigen and sets up an acute inflammation with release of cyto- kines and chemokines, which attract and activate microglia, and produce immunoglobulins that together culminate in damage to the myelin-oligodendrocyte unit. These inflammatory processes lead to disruption of the myelin membrane with increased spacing, ves- icular disruption, splitting, vacuolation, and fragmentation of the lamellae. Multiple sclerosis plaques can be classified into ‘acute’ or ‘chronic’, depending on the presence or absence of acute inflammatory cells. There are also different patterns of pathology. One scheme describes T cell infiltrates and macrophage associated tissue injury (pattern 1); antibody and complement-mediated immune reactions against cells of the oligodendrocyte lineage and myelin (pattern 2); hypoxia- like injury, resulting either from inflammation-induced vascular damage or macrophage toxins that impair mitochondrial function (pattern 3); and a genetic defect resulting in primary susceptibility of the oligodendrocytes to immune injury (pattern 4). The evidence for pathological heterogeneity, as opposed to complexity in which additional effector molecules are recruited to the evolving lesions following initial T cell infiltration of the CNS, has recently been challenged. Rather, the various pathological features are now seen as stages in the development of a ubiquitous pathological end-game, in which apparent heterogeneity may disappear over time as different pathways converge on one general mechanism of demyelination— the presence of complement, antibody and Fc γ-receptor on

 phagocytic macrophages, indicating that antibody dependent cell- mediated cytotoxicity is primarily responsible for demyelination in established multiple sclerosis. The focus on inflammation and demyelination had until recently obscured the extent and significance of neuronal and axonal injury. Axonal injury is present at all stages of multiple sclerosis. Recent recognition of the fundamental role

oligodendrocytes play in pro- viding metabolic support to axons through glial glycolysis products adds to the multiple mechanisms by which disruption and loss of the oligodendrocyte-myelin unit can lead to axonal injury and ul- timately neuronal loss. Key modes of injury that are now implicated, include glial-mediated production of reactive oxygen/nitric oxide species, mitochondrial injury, intra-axonal cation excess, altered astroglial environment, and cellular excitotoxicity. Early axonal in- jury evident by axonal transection and accumulation of amyloid precursor protein tends to occur when inflammatory demyelination is prominent. Whether the immune process directly targets axons or merely involves these structures as part of nonspecific collateral damage is unclear. Similarly, it is uncertain whether axonal loss in normal appearing white matter merely reflects axon dropout due to time-delayed Wallerian degeneration. Later, chronic axonal loss is associated with microglial activation throughout the brain paren- chyma and away from the postinflammatory chronic demyelinated lesions. In addition, several lines of evidence also implicate loss of oligodendrocyte-myelin-derived metabolic and trophic support as contributory to the mechanism of progressive neurodegeneration. The recognition that neurodegeneration is the dominant patho- logical substrate of progressive disability brings into focus the importance of understanding the relationship between focal lymphocytic inflammation—clinically manifest as relapses—and the neurodegeneration that drives the progressive phase of the dis- ease. A widely-held position is that inflammation drives the cascade of events leading to neurodegeneration, or conditions a genetic pre- disposition to axon degeneration that would not be exposed without the inflammatory trigger. Aetiology The aetiology of multiple sclerosis involves interplay between genes and the environment. It is a disease of northern Europeans and oc- curs less frequently in other racial groups. There is a female pre- dominance that may be increasing. The familial recurrence rate is approximately 15%. Meta-analysis among relatives of probands from three population-based series shows that the age-adjusted risk is highest for siblings (3%), then parents and children (2%), with lower rates in second- and third-degree relatives. Recurrence in monozygotic twins is around 35%. Conversely, the frequency of multiple sclerosis in adoptees is similar to the population risk for Europeans. The age-adjusted risk for half-siblings is intermediate between ‘social’ and biological relatives. Recurrence is higher in the children of conjugal pairs with multiple sclerosis (age-adjusted 20%) than the offspring of single affecteds (2%) (Fig. 24.10.2.2). Population studies carried out in the 1970s, demonstrated an as- sociation between the linked class II MHC alleles (DR15 and DQ6) and their corresponding genotypes. Extensive searches, using as- sociation and linkage studies over many years, until recently, had yielded very few additional candidates for susceptibility. However, Clinical neurological dysfunction Axonalloss Progressive stage Relapsing-remitting stage Relapsing with persistent deficits (a) Disease progression and axonal loss in multiple sclerosis Axonal loss Inflammation & demyelination Loss of oligodendrocyte /myelin signals (b) Contribution of demyelination to axonal loss Fig. 24.10.2.1 Inflammation, demyelination, axonal loss, and disease progression in multiple sclerosis. (a) The early stage of relapsing-remitting multiple sclerosis is characterized by transient neurological deficits that return to normal and pathology dominated by focal inflammation and demyelination. However, as the disease progresses neurological dysfunction becomes fixed and accumulates. The pathological correlate of the progressive phase of the disease is axonal loss. (b) The early events of demyelination and inflammation are believed to contribute to axonal loss by numerous mechanisms including loss of oligodendrocyte/myelin- derived trophic and structural support. The schematic diagram shows a single oligodendrocyte (black and white) myelinating three axons (axon purple, myelin blue). Early in the course of multiple sclerosis, the oligodendrocyte is damaged through inflammatory driven mechanisms resulting in demyelination of the axon. The

loss of oligodendrocyte contributes and culminates in axonal loss as found in progressive multiple sclerosis.

section 24 Neurological disorders 6030 recent large-scale genome-wide association studies involving tens of thousands of cases and controls have identified well over 100 loci that, individually, confer a modest increase in risk. Collectively these studies underline a central role for the immune system in the devel- opment of MS beyond the longstanding HLA association, as well as revealing that multiple sclerosis clusters with other autoimmune conditions. Functional studies of these genes are broadly lacking but it is of considerable interest that most of these genes are noncoding and frequently mapping to regulatory regions on immune cell types. This evidence from genetic analysis is one of the most compelling reasons for concluding that multiple sclerosis is primarily an im- munological disorder. Apart from informing ideas on the pathogen- esis of multiple sclerosis, within this list of over 100 susceptibility genes are several that inform current therapeutic strategies or sug- gest new approaches to treatment. For example, the variant respon- sible for the association between multiple sclerosis and TNFRSF1A confers functional properties on immune cells that increase their production of soluble TNFα, reproducing the pattern previously shown to increase disease activity after administration of anti-TNFα therapeutic antibody of TNFα-receptor blockade, illustrating the potential for pharmacogenomics to inform future treatment selec- tion and stratification. Ongoing genetic studies are aimed at dis- covery of further heritability genes with estimates of 30–50% still unaccounted, along with functional studies of known genes and fi- nally the role of genetics in determining disease course. Studies of concordance in multiplex families show that genetic factors influence the risk of progression but, as yet, no responsible loci are identified. Genetic analysis may also contribute to the de- bate on whether multiple sclerosis is one disease. Mutations of mito- chondrial DNA are responsible for a multiple sclerosis-like illness characterized by disproportionate involvement of the anterior visual pathway, although mitochondrial genes do not contribute generally to susceptibility in multiple sclerosis. A major part of future studies in the genetics of multiple sclerosis will be to resolve the question of disease heterogeneity. The distribution of multiple sclerosis cannot be explained only on the basis of population genetics. In white South African people and in Australia, prevalence rates are half those documented for many parts of northern Europe. There is a gradient in frequency, both in Australia and in New Zealand, which does not follow genetic clines. The risk is higher for English-speaking white people migrating into South Africa as adults than in childhood. Multiple sclerosis oc- curs at a low frequency in the Caribbean population, but the risk increases substantially in their first-generation descendants raised in the United Kingdom. Over and above the effect of racial predis- position, migration influences distribution of the disease. Surveys of multiple sclerosis have prompted speculation on the occurrence of post-Second World War epidemics in Iceland, the Orkney and Shetland Islands, and the Faroes, but others prefer the interpretation that these merely reflect improved case recognition. Noting the association with latitude, and other apparent epi- demiological features such as seasonality for month of birth in people who later develop multiple sclerosis, it has been suggested that the environmental effect is conferred by variable light exposure and vitamin D status. Without much in the way of mechanistic in- terpretation or compelling evidence, this has led to widespread self-prescribing of vitamin D among affected individuals, often con- doned by physicians. Probably harmless in small doses, it will never- theless take time to establish whether the hypothesis for a role of vitamin D, ubiquitously deficient in the normal population at risk of multiple sclerosis, is substantiated. A second risk factor that has some support from epidemiological and genetic studies is smoking. Here, the analogy with rheumatoid

arthritis in which proteins are shown to be abnormally citrullated following passage through the lungs of smokers has some mechanistic logic. The widely accepted formulation that multiple sclerosis is the outcome of unknown envir- onmental factors, conditioned by age at exposure, acting on a genet- ically vulnerable population has led to a largely unrewarding search for such environmental agents. However, the risk of developing multiple sclerosis is increased for individuals exposed to measles, mumps, rubella and (especially) Epstein–Barr virus infection rela- tively late in childhood or adolescence. These studies suggest that an age-linked period of susceptibility to viral exposure exists in those who are constitutionally at risk of developing the disease. Relationship Genetic sharing 100% 50% 25% 12.5% 0% MZ twin Sibling, 2 affected parents Sibling,1 affected parent DZ twin Sibling Parent Child Half sibling Aunt/uncle Nephew/niece Cousin Adoptee General population 0 5 10 15 20 25 30 35 Age-adjusted lifetime risk Fig. 24.10.2.2 Lifetime risk for multiple sclerosis among European people and in biological and social relatives of affected individuals. The increased risk with relatedness implicates genetic factors, whereas the incomplete concordance in identical twins reflects the contribution made by environmental conditions.

24.10.2 Demyelinating disorders of the central nervous system 6031 Symptoms and signs of multiple sclerosis Fatigue Difficult to define and capture for analysis, nonetheless fatigue is one of the most characteristic symptoms of multiple sclerosis. Patients report overwhelming lassitude after undertaking a physical or cog- nitive task, forcing them to stop and rest. However, they do not feel the need to sleep. Fatigue may occur acutely, in the context of a re- lapse, or be a persistent symptom. It may be disabling, particularly in individuals attempting to maintain demanding occupations or hobbies. Optic neuritis and visual symptoms Acute demyelinating optic neuritis is a first manifestation of mul- tiple sclerosis in up to 20% of patients. This presents with pain on eye movement, followed by subacute visual loss, which evolves over hours or days, sometimes to complete blindness; patients may be aware of selective loss of colour vision and flashes of light (phosphenes) on eye movement. Other signs of optic neuropathy at presentation include unilateral afferent pupillary defect and visual field loss. The pain disappears within a few days; vision begins to im- prove within 4 weeks and improves in 90% of patients over months, but defects of colour perception frequently persist. The lesion responsible for optic neuritis can be imaged in vivo; inflammation within the intracanalicular portion of the nerve and long lesions are associated with delayed or incomplete recovery of vision. Correlations between imaging, symptoms and neuro- physiological changes indicate that the visual deficits in optic neuritis arise at the time of altered blood–brain barrier perme- ability. They are associated with conduction block and precede demyelination or axonal degeneration. Optical coherence tom- ography provides a noninvasive quantitative measure of retinal nerve fibre loss after optic neuritis, and is increasingly being used as a surrogate outcome measure in treatment trials. Optic neur- itis may be clinically silent and revealed by delayed conduction of visual evoked potentials; this can be useful in the diagnosis of multiple sclerosis. Optic neuritis can be a feature of other conditions and clinicians should be aware of the red flags of: positive family history, bilateral onset, failure to improve or dependence on steroids (see next). It can be mimicked by acute glaucoma, infection (especially viral), ischaemic optic neuropathy, sarcoidosis, systemic lupus erythematosus, and vasculitis. Visual failure in Leber’s hereditary optic neuropathy can mimic bilateral sequential optic neuritis in men, so a family history of mitochondrial inheritance should be sought. The postchiasmal visual pathway is occasionally involved in mul- tiple sclerosis resulting in hemianopic field defects. Motor symptoms and signs Impaired mobility affects most patients with multiple sclerosis, usu- ally as a result of

spinal cord disease. Movements are slow, weakness differentially affecting extensors in the arms and flexors in the legs, and there are the expected signs of upper motor neurone lesions. Spasticity may be more problematic than weakness and all aspects of immobility are frequently complicated by fatigue. Cerebellar in- volvement causes incoordination of speech, bulbar control, eye movements, the individual limbs, or balance, usually in combin- ation with corticospinal damage. Damage to the superior cerebellar peduncle or red nucleus produces a disabling proximal wild flinging tremor. Parkinsonism does not occur in multiple sclerosis. Lower motor neurone signs occur when there is extensive demyelination adjacent to the dorsal root entry zone. Sensory symptoms and signs Altered sensation occurs at some stage in nearly every patient with multiple sclerosis, usually due to partial disruption of the spinal cord sensory pathways. Often they are described in complex and graphic terms: ‘as though water is dripping down my face’, ‘it feels as though something is twisting a towel repeatedly around my legs’. Damage to the posterior columns in the cervical cord produces tight, burning, twisting, tearing, or pulling sensations, which are usually unpleasant. Associated loss of proprioception severely com- promises function. Spinothalamic tract involvement leads to loss of thermal and pain sensation. The commonest physical sign found in multiple sclerosis, in the absence of symptoms, is impaired vibra- tion sense in the legs. Autonomic involvement Autonomic symptoms occur in most patients with multiple scler- osis. Bladder symptoms are common and can be due to impaired bladder emptying (leading to urinary retention) or filling (leading to urgency and hesitancy). Often these coexist. Impaired control of the rectal sphincter is much less common. Erectile impotence oc- curs frequently in males and is usually a manifestation of spinal cord disease. Mechanical difficulties, spasticity, altered sensation, skin ex- coriation, and indwelling catheters all may affect sexual fulfilment, in both genders. Other autonomic features in multiple sclerosis occur rarely, but include loss of thermoregulation leading to in- appropriate sweating, fever, and hypothermia; Horner’s syndrome; abnormalities of cardiac rhythm and vascular responses with acute pulmonary oedema; weight loss; and inappropriate secretion of vasopressin. Eye movements Abnormalities of eye movement are frequent in multiple sclerosis. A sign that is nearly always due to multiple sclerosis, and is usually asymptomatic, is the ‘internuclear ophthalmoplegia’: slowness of the adducting eye and nystagmus in the abducting eye on horizontal gaze, due to a lesion of the medial longitudinal fasciculus. It is often bilateral and may coexist with gaze paresis to produce the ‘one and one-half’ syndrome. They commonest sign is first-degree symmetrical horizontal jerking nystagmus. Weakness of the lateral rectus is more common than isolated third and fourth nerve palsy. Vertical up-beating nystagmus can occur and is often associated with bilateral inter- nuclear ophthalmoplegia. Down-beating nystagmus may occur, but is a red flag for alternative, structural causes. Ocular flutter (hori- zontal saccadic oscillations without an intersaccadic interval) and opsoclonus, in which the saccadic movements occur in all direc- tions, tend to occur late in multiple sclerosis and can be visually disabling. Other brainstem manifestations Feelings of unsteadiness are common. Acute brainstem demyelin- ation causes severe positional vertigo, vomiting, ataxia, and head- ache. Taste may be subjectively abnormal but ageusia is rarely

 described. Deafness may occur in multiple sclerosis, but is a red flag for other conditions (Susac’s and Cogan’s syndromes). Facial weakness, indistinguishable from Bell’s palsy, occurs in patients with multiple sclerosis, alone or in association with other signs of brainstem disease, including hemifacial spasm and diffuse rippling of muscle fibres (myokymia). Exceptionally, there may be unilateral involvement of the hypoglossal and recurrent laryngeal nerves. Extensive brainstem demyelination may produce disturb- ances of consciousness and

respiratory failure. Occasional mani- festations include the locked-in state, persistent hiccup, and lateral medullary syndrome. Paroxysmal symptoms are invariably brief, but repetitive and usu- ally occur in bouts lasting a few weeks or months before remitting. Symptomatic trigeminal neuralgia may begin in the first division or bilaterally, at a younger age than the idiopathic condition, and with associated signs of trigeminal involvement including motor weakness and sensory loss. It is usually associated with demyelinating lesions of the dorsal root entry zone, but may coexist with compression of the fifth cranial nerve by ectatic vessels. Other than trigeminal neuralgia, isolated involvement of the fifth nerve is rare. Paroxysmal dysarthria and ataxia with a clumsy arm, complex disturbances of sensation, and painful tetanic posturing of the limbs lasting 1 or 2 min are often triggered by movement and preceded by positive sensory symptoms on the side opposite to the muscular spasm. These are easily recog- nized and treated. Bursts of pain and paraesthesias, sensory distor- tion, itching, cough, and hiccup, painful extensor spasm, akinesia, kinesogenic choreoathetosis, and complex gaze palsies—any of which may respond to anticonvulsants, especially carbamazepine— also appear to be paroxysmal manifestations of multiple sclerosis. Cognitive and affective symptoms Cognitive impairment occurs in up to 65% of patients with mul- tiple sclerosis. It may occur at all stages of the disease, and be compounded by cognitive fatigue and depression. Reductions in attention, information processing speed, working memory, and ex- ecutive functions are typical and likely reflect both a white matter disconnection syndrome, as well as increasingly recognized cortical structural abnormalities. Specific cognitive deficits due to hypothalamic involvement, including the Korsakoff state and the syndrome of bulimia, lack of social restraint, apathy, and mutism are sometimes seen. Discrete cortical syndromes, such as aphasia, are rare and should prompt in- vestigation for other causes. Depression occurs more frequently in multiple sclerosis than in patients with comparable neurological disability; hypomania is occasionally seen, but should not be confused with pathological laughter and crying, arising from loss of central inhibition of facial and bulbar reflexes in association with extensive brainstem disease. Psychosis is rarely a feature of multiple sclerosis. Rare manifestations of multiple sclerosis The list of rare clinical manifestations (some already described) includes massive cerebral lesions, aphasia, headache, fever, move- ment disorders, epilepsy, hypothalamic and pituitary symptoms, re- spiratory failure, and peripheral neuropathy. Narcolepsy, Sjögren’s syndrome, ankylosing spondylitis, type I neurofibromatosis, and autoimmune thyroid disease have periodically been associated with multiple sclerosis. Childhood multiple sclerosis 2% of patients with multiple sclerosis present before the age of 10, and up to 10% before 16 years. Fever and meningism, impaired con- scious level due to cerebral oedema with swollen optic discs, and seizures are regular features and the distinction from acute dis- seminated encephalomyelitis can often only be made by the later occurrence of relapse and remission. A recent European study of the natural history of childhood onset disease confirms a higher fe- male to male ratio (3:1), disease course that is invariably relapsing- remitting and a delayed time by 10 years to secondary progression compared with adult-onset disease. Current international guide- lines recommend disease-modifying treatment for childhood ac- tive relapsing-remitting multiple sclerosis on lines similar to adult patients. Clinical course and prognosis Most patients present as a young adult. In many, a history of symp- toms attributable to demyelination may be elicited from years earlier. But where this is not the case, patients are said to have a ‘clin- ically isolated syndrome’ (Fig. 24.10.2.3) and magnetic resonance imaging discriminates disease that is ‘active’, indicating a high prob- ability of further clinical attacks, or ‘inactive’. The latest diagnostic criteria (Table 24.10.2.2) would classify someone in the active group as having ‘multiple sclerosis’ already. The subsequent illness passes through the three phases of relapse with full recovery, relapse with persistent deficits, and

secondary progression (Fig. 24.10.2.1). There is considerable variation in how rapidly people progress through these phases, but typically sec- ondary progression starts around the age of 40 years. In the minority 20%, a ‘primary progressive’ syndrome starts also around the age of 40, but without preceding relapses. Few (perhaps 5%) escape dis- ability and are classified as having ‘benign multiple sclerosis’. It is very rare to die directly from demyelination of the nervous system (although possible with, for instance, a large brainstem plaque), but the secondary effects of disability associated with the disease reduce life expectancy by around 10 years. Relapses build up over days or a few weeks and then plateau before recovery, partial or complete, occurs over weeks or months. They are most frequent (less than once a year) at the outset of the disease and Clinically isolated syndrome Relapsing-remitting multiple sclerosis active inactive active inactive Fig. 24.10.2.3 Early multiple sclerosis may be classified on the basis:
(i) of the number of attacks, for exmple, clinically isolated syndrome where there has been only one clinical attack and relapsing-remitting multiple sclerosis for two or more episodes; and (ii) of activity, defined by one or more relapses, or one or more new MRI lesions, over a 12-month period. Under the McDonald criteria, the ‘active’ form of clinically isolated syndrome may be re-classified as multiple sclerosis.

 decrease steadily thereafter. Some 25% of relapses are triggered by an infection, especially upper respiratory and gastrointestinal; but careful studies have shown that vaccinations do not induce attacks. Major life events, such as bereavement, increase the risk of a re- lapse. The timing of relapses, but not the overall relapse rate, is al- tered by pregnancy. There is a reduction in the prepregnancy relapse rate for each trimester, balanced by a threefold higher risk in the puerperium. The clinical course is uninfluenced by breast feeding or anaesthesia. There is no evidence that trauma influences multiple sclerosis. Counterintuitively, there is only a weak relationship between re- lapse rate and a patient’s long-term prognosis. The strongest prog- nostic factor is a short interval between the initial episode and first relapse. Classical rules are that the prognosis is relatively good when sensory or visual symptoms dominate the illness and there is com- plete recovery from individual episodes; conversely, motor involve- ment, especially when co-ordination and balance are disturbed, has a less good prognosis. Once progressive multiple sclerosis has started, either primary or secondary, it proceeds relentlessly. Its onset is largely age-related, at the age of 40 years, and its rate is similar between individuals and unrelated to previous disease history or relapse rate. These obser- vations raise unresolved questions around the relationship between inflammation, manifesting as relapse, and neurodegeneration, the primary substrate of progression. The nature of the disability that progresses in ‘secondary progres- sion’ reflects areas of previous damage in relapses. Usually it is the spinal cord that bears the brunt of progressive multiple sclerosis, but optic nerve, cerebral, and brainstem disease may also advance slowly. Primary progressive spinal disease is the usual mode of pres- entation when multiple sclerosis develops beyond the fifth decade. It is characterized by an absence of acute attacks with gradual de- cline from onset and, although cerebrospinal fluid analysis is similar to relapsing-remitting disease, there are comparatively more spinal and fewer brain abnormalities on MRI. Current disease-modifying agents have no demonstrable effect on primary progressive disease.
Investigations Multiple sclerosis can reliably be diagnosed using clinical criteria and without laboratory support. There is no single diagnostic laboratory investigation, but they can be used to demonstrate the anatomical dissemination of lesions; to provide evidence for intra- thecal inflammation; to demonstrate that conduction is altered in a form consistent with demyelination;

and to exclude conditions that mimic demyelinating disease. Magnetic resonance imaging Variations in the imaging protocols are beginning to distinguish separate components of the underlying pathological process. Imaging can highlight inflammation (gadolinium–DTPA enhance- ment of T1-weighted lesions, indicating that the lesion is of recent origin), demyelination and remyelination (magnetization transfer ratio), astrocytosis (T1-weighted lesions, the signal arising from increased water content), and axonal damage (reduction in dif- fusion tensor imaging anisotropy and N-acetyl-aspartate spectra with chemical shift imaging, or the presence of focal atrophy and T1-weighted black holes; see Fig. 24.10.2.4). The evolving lesion starts with increased blood–brain barrier permeability, which lasts for up to four weeks, and is revealed by demonstration of enhance- ment after intravenous gadolinium. These lesions may disappear Table 24.10.2.2 Diagnosis of multiple sclerosis (McDonald 2011 criteria) History Examination Dissemination in space demonstrated by: Dissemination in time demonstrated by: Relapsing-remitting multiple sclerosis Two clinical episodes compatible with demyelination Signs of two or more anatomical sites affected Examination History Two clinical episodes compatible with demyelination Signs of only one anatomical site affected MRI. More than one lesion in at least two of 4 typical sites for multiple sclerosis plaques History One clinical episode compatible with demyelination Signs of only one anatomical site affected MRI. More than one lesion in at least two of 4 typical sites for multiple sclerosis plaques MRI. Either simultaneous presence of lesions of different age at presentation, or new lesions on a second MRI scan at any time after the first Primary progressive multiple sclerosis One year of progression of a typical syndrome (spinal, cerebellar) 2/3 of:

1. MRI lesions in at least two of 4 typical sites for multiple sclerosis plaques
2. More than one spinal cord lesion on MRI
3. Ccerebrospinal fluid oligoclonal bands Fig. 24.10.2.4 Typical plaques of multiple sclerosis in a MRI brain and cord. Note the periventricular, callosal and juxtacortical lesions in the brain and that the spinal cord lesions are no greater than one vertebral segment in length.

section 24 Neurological disorders 6034 but reactivation is sometimes seen, the cycles lasting about 8 weeks. Fluid attenuated inversion recovery (FLAIR), proton-density, and T2 sequences best demonstrate demyelination. The periventricular lesions, which characterize multiple sclerosis, correlate with areas of persistent demyelination and astrocytosis. A mixture of new, evolving, and recovering lesions may be seen in an individual pa- tient at any one time. Magnetic resonance lesions occur about 10 times more frequently than new clinical events. Eventually, there is a reduction in the frequency of new lesions as patients move from the relapsing to progressive phases of the disease and evidence for at- rophy is then more apparent. The number or volume of lesions cor- relates poorly—if at all—with disease severity or course, but there is less cerebral involvement in patients who present with primary pro- gressive disease compared with those with similar disability from secondary progression. Progressive loss of brain volume—occurs at a rate of 0.5–1.0% p.a. in patients with multiple sclerosis, com- pared to a rate of 0.1% p.a. in age-matched controls—is also quan- tifiable using T1-weighted MR brain-imaging and is increasingly utilized as an outcome measure in trials of putative neuroprotective agents. Brain atrophy is significantly correlated with disability and cognitive impairment in multiple sclerosis. However, the imaging abnormalities of multiple sclerosis are not specific and similar changes occur with other inflammatory or vascular lesions and with advancing age. MRI scans are used in the diagnosis, prognosis, and treatment of multiple sclerosis. In diagnosis, they are first used to determine the

pathology of the lesion causing current symptoms, whether structural or not. For instance, it is mandatory to scan the spinal cord of someone presenting with a myelopathy. Secondly, scans are used to identify ‘dissemination of lesions in space’, that is to show the presence of other (asymptomatic) lesions in the brain or spinal cord. Thirdly, MRI scans can also be used to demonstrate ‘dissemination of lesions in time’. If a patient has had several dis- crete clinical episodes of demyelination over time, this is not ne- cessary. But, for those patients with a clinically isolated syndrome, new lesions that appear on interval scans mean that ‘multiple sclerosis’ can be diagnosed (Table 24.10.2.2). This process can be further contracted; a MRI brain with lesions of different ages (for instance, some with and some without gadolinium enhancement) is sufficient to establish ‘dissemination in time’ and diagnose mul- tiple sclerosis at the time of a clinically isolated syndrome. MRI scans are useful in guiding prognosis in the clinically iso- lated syndrome. If there are no brain lesions at presentation, the chance of having a second demyelinating clinical episode over 20 years is only 20%. However, this rises to 80% if the initial brain MRI shows three or more plaques. There is a consensus, perhaps more than justified by the evidence, that rapid accumulation of MRI lesion load is a poor prognostic sign in multiple sclerosis. It is intuitive that the early appearance of brain atrophy is also a poor sign, although this has not yet become a routine clinical MRI measure. In determining the response to treatment it is established that new MRI lesion formation during the first year of first-line disease- modifying treatments, is a biomarker for a poor disability outcome. It is logical to consider augmenting treatment as a result, but while this can be effective in substantially reducing or even eliminating further radiological ‘events’, the long-term effect on disability re- mains uncertain. Cerebrospinal fluid With the increasing availability and sophistication of magnetic res- onance imaging, confidence in making the diagnosis of multiple sclerosis with supportive imaging alone has risen and fewer lumbar punctures are performed. There are two situations where they are commonly done: in patients over the age of 50 years (where non- specific lesions obscure the ability of MRI scans to discriminate de- myelination) and to diagnose primary progressive multiple sclerosis. The cerebrospinal fluid cell count rarely exceeds 50 lymphocytes/ ml, even during periods of clinical activity, and is normal in more than 50% of patients. There is a rise in total protein (usually <1 g/l), with a specific increase in the immunoglobulin concentration. The most characteristic abnormality is the presence of oligoclonal im- munoglobulin bands on protein electrophoresis in the cerebrospinal fluid and not in the serum. This pattern is seen in more than 90% of patients and its absence is a ‘red flag’ for an alternative diagnosis. Despite their ubiquity, the relationship of this intrathecal synthesis of immunoglobulins to disease pathogenesis is mysterious. Electrophysiology Demyelination in pathways can be detected using visual, auditory, somatosensory, central motor, and event-related potentials; charac- teristically their latencies are delayed but amplitudes are unaffected. Their main use is to detect involvement of clinically unaffected path- ways and so show ‘dissemination of space’. Optical coherence tomography Optical coherence tomography (OCT) is a noninvasive imaging technique that uses back-scattered infrared light to detect the ret- inal layers. Thinning of the retinal nerve fibre layer is seen in mul- tiple sclerosis and the degree of thinning, reflecting axonal loss, is associated with quantitative measures of visual impairment. More recently introduced high resolution spectral-domain OCT can also measure the retinal nerve ganglion cell and inner plexiform layer, and thinning, reflecting ganglion cell loss, is significantly correlated with measures of visual dysfunction. OCT is a rapid, noninvasive, and increasingly used measure to provide quantitative and longitu- dinal measures of retinal neuronal status that potentially also serves as a surrogate for wider CNS neuronal health. Differential diagnosis The commonest error in clinical practice is to make the diagnosis of multiple sclerosis in patients with progressive spinal disease in

whom a structural lesion has not been adequately excluded. Rarely, a spinal tumour presents with intermittent symptoms creating dif- ficulties for the unwary; it is not safe to assume the diagnosis of multiple sclerosis in patients with symptoms and signs restricted to a single site, whatever the clinical course, without appropriate in- vestigation. Lesions at the foramen magnum are particularly well placed to cause confusion through appearing to produce evidence for independent spinal and brainstem lesions. Errors also arise with progressive and relapsing manifestations of brainstem or spinal ar- teriovenous malformations. Care must be taken in the diagnosis of multiple sclerosis when several members are affected within one family. Hereditary spastic paraplegia mimics familial multiple sclerosis and this should also be considered in isolated cases of progressive spastic para- plegia, when pyramidal manifestations occur in isolation and

 with disproportionate spasticity. Other familial disorders con- fused with multiple sclerosis, include the hereditary ataxias, adult- onset leukodystrophies (see next) and vasculopathies (CADASIL). Pedigrees with affected males and maternal inheritance may be ex- amples of X-linked adrenoleucodystrophy, and the phenotype of multiple sclerosis occurs in families with the clinical and genetic features of Leber's hereditary optic atrophy. Clinical, immunological, and imaging abnormalities indistin- guishable from multiple sclerosis occur with granulomatous and vasculitic diseases of the brain, especially the cerebral variant of systemic lupus erythematosus, which often occurs in the absence of systemic manifestations, although headache and prominent cogni- tive impairment are clues to a vasculitic aetiology. Sarcoidosis may present with clinical involvement of the central nervous system, typ- ical magnetic resonance and cerebrospinal fluid abnormalities, and without pulmonary or cutaneous manifestations; uveitis also occurs in multiple sclerosis and so is not necessarily a useful discriminator. Orogenital ulceration in a patient with the clinical manifestations of multiple sclerosis suggests the diagnosis of Behçet's disease. Alternative diagnoses need to be considered when multiple scler- osis is diagnosed in African or Asian people in whom progres- sive spinal disease, sometimes with visual involvement, is more probably due to HTLV1-associated tropical spastic paraplegia or neuromyelitis optica. Infections of the nervous system can mimic the isolated demyelinating syndromes and multiple sclerosis. These include tuberculous and other chronic meningitides, and the neuro- logical manifestations of acquired immunodeficiency syndrome and Lyme disease, which can also cause a chronic or relapsing disorder of the central nervous system, but which is usually preceded by a characteristic painful polyradiculitis and facial palsy. Similarities be- tween multiple sclerosis and neurosyphilis should not be forgotten in the context of opportunistic infection complicating HIV infec- tion. The age distribution and clinical manifestations usually make it easy to distinguish subacute combined degeneration of the spinal cord from multiple sclerosis, but focal spinal lesions, accompanied by Lhermitte's sign, occur in vitamin B12 deficiency. Treatment of demyelinating disease Therapies in multiple sclerosis are aimed at managing individual symptoms, resolving acute attacks, preventing new relapses, limiting disability, and (for the future) preventing progression and repairing the damage. Symptomatic management The complex and progressive nature of disability requires a multi- disciplinary approach to patients with multiple sclerosis. Several manifestations of the disease can be treated successfully. The first step in managing bladder symptoms is a postmicturition bladder volume assessment: if less than 100 ml, urgency and frequency of micturition can be treated with anticholinergic drugs (oxybutinin or terodoline), whereas a volume greater than 100 ml requires clean self-intermittent catheterization, which is easily adopted by motiv- ated patients retaining adequate visual and arm function. It ensures complete bladder emptying, often with unimagined

advantages to social activities and sleep. Other options include intravesical botox injections to reduce reflex bladder contractions or a suprapubic catheter with closure of the lower urinary tract, which is preferable to an indwelling urethral catheter or, worse still, constant dribbling incontinence, which usually leads to skin excoriation. These man- oeuvres have largely replaced urinary diversion through an ileal conduit, insertion of an artificial mechanical sphincter, or electrical stimulation of the spinal nerve roots in an attempt to synchronize sphincter contraction and relaxation. Constipation in multiple sclerosis is managed by dietary alteration and the use of bulk laxatives. Loperamide may be useful where the predominant complaint is rectal urge incontinence. Psychological factors contribute to impotence in males with multiple sclerosis, but in most cases the complaint is a direct consequence of spinal demyelination, and usually well treated with sildenafil—a phospho- diesterase inhibitor which acts by increasing local production of ni- tric oxide in response to sexual stimulation. Spasticity causes pain and, in more disabled patients, can inter- fere with personal care. Baclofen, a GABA agonist acting on spinal cord reflexes, is still the most widely used effective antispastic agent. The principal adverse effect, like most conventional antispasticity agents, is sedation and increased weakness. Gabapentin introduced as an anticonvulsant, but now more frequently used to relieve neuro- pathic pain, is also effective. Benzodiazepines reduce spasticity by increasing presynaptic spinal inhibition. Dantrolene sodium acts by uncoupling excitation–contraction mechanisms in individual muscle fibres. Tizanidine, an α-2 agonist that modulates activity of excitatory presynaptic interneurones, may reduce spasticity without increasing weakness. Intrathecal baclofen can be more effective than systemic administration, delivering a greater concentration of drug to the target cord reflexes, but carries the disadvantage of an implanted device, prone to failure and infection. It is mainly ap- propriate for patients with advanced disease. Targeted reduction in focal spasticity is achievable with local injection of botulinum toxin. There may be a role for surgical interruption of the reflex pathways or tenotomy and peripheral nerve block with phenol or alcohol. Tremor is very difficult to treat, although some improvement may be seen with β-blockers; alternatives include anticonvulsants, isoniazid, ondansetron, and hyoscine. Physical restraint is rarely successful. Stereotactic procedures involving stimulation of the ventrolateral nucleus produce results comparable to destructive pro- cedures, but the dividend is small. Unsteadiness arising from altered vestibular input may improve with the use of a vestibular sedative. Fatigue as a dominant symptom in multiple sclerosis is common and frequently disabling, although its pathophysiological basis is poorly understood. It may well be multifactorial and compounded by depression. Some evidence suggests improvement with amantadine or modafanil. The paroxysmal manifestations of multiple sclerosis usually stop abruptly with the use of carbamazepine or gabapentin; this and other anticonvulsants, especially gabapentin, may also relieve tri- geminal neuralgia or the more refractory forms of pain arising from spinal demyelination. Nerve block and chemical or surgical destruc- tion of nerve fibres are sometimes an acceptable method for redu- cing pain in multiple sclerosis. All these sensations are coped with less well in the context of impaired mood and can respond usefully to antidepressants. For those who develop significant disabilities and impairments, comprehensive care includes access to physical and occupational therapists, social workers, and other health-care staff with expertise in the management of chronic neurological illness. Complications are best prevented by awareness and anticipation since they usually

 develop quickly yet take months to resolve. Minimizing handicap by attention to social, vocational, marital, sexual, and psychological aspects of the illness is more important for many patients than drug treatment. In situations where the natural history

has already led to loss of mobility, the early use of mechanical aids and home adapta- tions should be encouraged despite the associated stigma. Management of the acute episode Corticosteroids are effective in reducing the duration of acute demyelinating episodes in multiple sclerosis and related disorders, but have no impact on the eventual degree of recovery or the subse- quent disease course. So their use is restricted to relapses which are painful or disabling. There is no evidence that intravenous steroids offer any advantage over oral, so the common prescription is oral methylprednisolone 500–1000 mg, daily for 3–5 days. Among patients with steroid-resistant relapses, 50% will improve with plasma exchange. These responders have been shown at biopsy to have lesions characterized histologically by immunoglobulin de- position and complement activation, but these patients cannot be identified prospectively. There is no evidence for reduction in re- lapse frequency or long-term disability using either corticosteroids or plasma exchange. Disease-modifying treatment in multiple sclerosis Multiple sclerosis has two distinct clinical phases, each re- flecting a dominant role for interrelated pathological processes. Inflammation drives activity during the relapsing-remitting stage and neurodegeneration represents the principal substrate of pro- gressive disability. Current disease-modifying agents target the in- flammatory component and are effective at reducing relapse rate and the accumulation of disability over the medium term (3–5 years); evidence beyond that is less robust. In contrast, there are no proven therapies for progressive disease independent of relapses. The first drugs to be licensed for multiple sclerosis, in the 1990s, were the injectable treatments, the β-interferons and glatiramer acetate. These are still used, because of their excellent safety record. But the newer therapies are either more efficacious or more con- venient (for instance oral treatments). Roughly speaking (see Fig. 24.10.2.5), the more efficacious drugs are also associated with more safety concerns. A simple classification scheme, from the Association of British Neurologists, is of two classes of drug: those of ‘moderate efficacy’ (β-interferons glatiramer acetate, teriflunomide, dimethyl fu- marate, and fingolimod) and drugs of ‘high efficacy’ (alemtuzumab, natalizumab, and ocrelizumab). β-interferons (Rebif®, Avonex®, and Betaseron®) and glatiramer acetate (Copaxone®) are administered subcutaneously or intramus- cularly, are generally well tolerated and reduce relapse frequency by around 30%. They somewhat reduce the accumulation of dis- ability for people with relapsing-remitting multiple sclerosis, but— perhaps surprisingly—do not have a long-term effect on disability when given earlier in the course of the disease, at the stage of the clinically isolated syndrome. Their mechanism of action is poorly understood. The interferons were first used because of their antiviral action, but their reduction of lymphocyte migration, Th17 expres- sion, and microglial class II expression is more likely. It is claimed that glatiramer, a random mixture of amino acids, acts by specific- ally suppressing antimyelinn lymphocytes. Teriflunomide is a pyr-imidine synthesis inhibitor that exerts selective antiproliferative effects on activated lymphocytes; it is as effective as the interferons and its main advantage is that it is taken orally. Fingolimod was the first oral drug approved for multiple scler- osis. It is a fungal derivative that upon phosphorylation acts as a sphingosine receptor agonist and nonspecifically limits lymphocyte egress from lymphoid organs. Dimethyl fumarate has two likely modes of action; anti-inflammatory through its suppression of nu- clear factor-κβ and antioxidative due to activation of the nuclear factor like 2 transcriptional pathway. Fingolimod and dimethyl fu- marate are preferable to the interferons because they are available as tablets and are more effective at reducing relapse frequency, per- haps by up to 50%. But this increased efficacy comes with higher risk: of gastrointestinal symptoms with dimethyl fumarate, and Alemtuzumab Natalizumab for JC neg patients Natalizumab for JC+ positive patients Fingolimod Dimethyl fumarate Increasing efficacy Glatiramer Teriflunomide Interferon-β Increasing burden of treatment (worse safety, more difficult

administration) Fig. 24.10.2.5 A simplified scheme of the risk-benefit analysis of current licensed disease-modifying therapy. Note that the risk of progressive multifocal leucoencephalopathy with natalizumab treatment rises from 1:10 000, if the patient is John Cunningham (JC) virus serology negative, to as high as 1:100 if positive and on prolonged treatment.

24.10.2 Demyelinating disorders of the central nervous system 6037 first-dose bradycardia, macular oedema, opportunistic viral infec- tions, and increased skin malignancy risk with fingolimod. Both are also associated with a very low risk of progressive multifocal leukoencephalopathy (see next). The advent of humanized monoclonal antibodies allows se- lective treatments targeting discrete stages in the immune- pathogenesis of multiple sclerosis. Two are currently licensed (natalizumab and alemtuzumab). Natalizumab is a recombinant antibody, delivered by monthly infusion, that prevents activated T cells entering the brain by binding to leucocyte α4 integrin. It is highly effective, reducing relapse frequency by 80%, and nor- mally very well tolerated. However, its use is associated with pro- gressive multifocal leucoencephalopathy, an opportunistic CNS infection due to John Cunningham (JC) virus, which is often fatal. The overall risk of progressive multifocal leucoencephalopathy with natalizumab use is 0.1%, but this risk can be personalized; it is highest, up to 2%, in those with a high concentration of anti- JC virus antibodies, who have received immunosuppressants prior to natalizumab, and who have been exposed to the drug for more than two years. Alemtuzumab works differently: it targets and de- pletes lymphocytes. It is given by intravenous infusion daily for five days, then a second cycle of three days is given at month 12, and then re-treatments are given only with evidence of break through disease. The aim is to reconstitute an immune repertoire that is no longer autoreactive for myelin. Alemtuzumab reduces the relapse rate by 80–90% and is the first drug to show consistent superiority against an active comparator (interferon-β-1a) across clinical and MRI measures. It is not associated with progressive multifocal leukoencephalopathy, but does cause a range of autoimmune dis- eases (thyroid in 30%, immune thrombocytopenia in 2% and renal disease in 0.1%). Several monoclonal antibodies are close to licensing. Daclizumab, targeting the CD25 antigen, reduces the activity of T lymphocytes and increases CD56 regulatory NK cells, and is proven more effica- cious than β-interferon. B-cell depletion with rituximab or its fully humanized equivalent, ocrelizumab, have shown highly significant reductions in clinical and radiological activity. Ocrelizumab has the distinction of being the only drug to have reduced the accumula- tion of disability in progressive multiple sclerosis, in a phase 3 trial. However, the trial population was not typical for progressive disease, in being enriched for patients with a high inflammatory load. The most radical, and efficacious, treatment for multiple sclerosis is autologous haematopoietic stem cell transplantation. However, it also has the most significant toxicity, with mortality of 2% in most large series and significant morbidity around the time of the trans- plant. Thus, it is not considered appropriate as a routine treatment of multiple sclerosis. Timing and sequencing of immunotherapy
in multiple sclerosis Stepping back from individual drug analyses, it is clear that a growing range of immunological therapies is becoming available, with varying efficacy and toxicity. All are agreed that early treatment will lead to optimum outcomes, and that immunotherapies are inef- fective in the progressive phase. However, there is not yet a consensus on how early and how ag- gressively multiple sclerosis should be treated. In the United States and most European countries, it is routine to start β-interferons or glatiramer acetate in all cases of clinically isolated syndrome; but long-term follow-up of trials of this approach does not demonstrate an effect on the accumulation of disability over placebo. In the more conservative United Kingdom, such treatments are only given

with ‘active CIS’ (Fig. 24.10.2.3). Although permitted by current EU li- censing, alemtuzumab is rarely used in this situation. Not all patients with relapsing-remitting multiple sclerosis have sufficiently active disease to justify the risks and inconvenience of treatment. A consensus view is that people with fewer than two relapses in the preceding two years may reasonably remain off treatment. There is also debate about how to sequence disease-modifying treatment. Those proposing an ‘escalation’ approach start with safer drugs, and only introduce more effective treatments if there is break- through disease activity. Alternatively, the ‘induction’ approach uses the most efficacious drugs first line; this gives greatest dividends in terms of preventing disability worsening, but raises the dilemma of exposing individuals who may never develop disability to the unpredictable hazards of prolonged immunosuppression. A key determinant in these negotiations is the patient’s attitude to the un- certainty of their prognosis and the risks of therapy. Therapies may be switched because of adverse effects or lack of efficacy. Neutralizing antibodies occur against the β-interferons (5– 40% depending on the formulation), and rarely against natalizumab and alemtuzumab. The increasing risk of progressive multifocal leucoencephalopathy with prolonged exposure to natalizumab often leads to switching (to fingolimod or alemtuzumab) despite main- tained efficacy. Once patients have entered the secondary progressive phase or become wheelchair bound, immunotherapies have no useful effect, although stopping therapy needs to be broached compassionately. Neuroprotection and repair strategies A body of evidence supports the hypothesis that chronically de- myelinated axons, devoid of myelin-derived support, are vulner- able to degeneration. Spontaneously remyelinated plaques show no significant axonal injury compared with inactive demyelin- ated lesions. Together with the recognition that spontaneous remyelination contributes to restoration of structure and function and that neurodegeneration underlies progressive disability, this supports the idea that myelin repair will prove neuroprotective. Two approaches are under consideration. In the first, oligodendrocyte precursors or neural stem cells are injected into the brain or cere- brospinal fluid. In the second, small molecules are used to promote endogenous remyelination by oligodendrocyte precursors already present in the brain. A parallel strategy is to interfere with the mechanisms underlying the neurodegeneration which follows demyelination noting that there is a consensus that ‘maladaptive ionic’ response to demye- lination sets in train a negative cycle of energy failure and linked processes, including reactive oxygen species production by glia, mitochondrial inhibition and likely convergence around a common process of intra-axonal cation excess that initiates secondary cal- cium mediated injury and ultimately death cascades, including excitotoxicity. For instance, sodium channel blockade may reduce the sodium influx that follows sodium channel redistribution. Perhaps this explains how phenytoin can slightly reduce the nerve cell damage following optic neuritis. Other agents that are believed

 to be beneficial through pleiotropic mechanisms, including statins are also under clinical trial in the progressive phase of disease. Other inflammatory demyelinating disorders Neuromyelitis optica spectrum disorder Neuromyelitis optica (NMO), originally known as Devic’s disease, was considered a variant of multiple sclerosis until its very different pathogenesis and prognosis was recognized in the early 2000s. The prototypical form is the simultaneous appearance of severe bilat- eral optic nerve and spinal cord inflammation. But the discovery of a biomarker (‘anti-aquaporin 4 antibodies’) has led to expansion of the phenotype. The unifying term ‘NMO spectrum disorder’ (Table 24.10.2.3) is now used for a condition which can include demyelination of the optic nerve, spinal cord, area postrema, and other brainstem, diencephalic, or cerebral sites. The target of the common pathogenic antibodies in neuromyelitis

optica are the water channels, aquaporin-4, which are particularly present in the foot processes of astrocytes. Complement-mediated death of the astrocytes leads to secondary loss of oligodendrocytes and neuronal injury. A minority of cases of neuromyelitis optica have circulating antibodies to myelin-oligodendrocyte glycoprotein (MOG). Compared to multiple sclerosis, episodes of neuromyelitis optica are more severe and lead to greater residual disability but, for reasons which are unclear, do not lead to secondary progressive disability. Optic neuritis and myelitis may occur simultaneously or sequentially, which would be unusual in multiple sclerosis. Hiccups, persistent vomiting, and painful sensory symptoms are also seen more frequently in neuromyelitis optica. The cerebro- spinal fluid lacks oligoclonal bands. On MRI, the spinal lesion is 'longitudinally extensive myelitis', extending over three or more vertebral segments and involving the whole cross-section of the cord, in contrast to multiple sclerosis plaques, which occupy one to two vertebral segments in length and only part of the cross- sectional area. The MRI brain may be normal, show symmetrical bilateral diencephalic lesions or large cortical lesions. Although disability may be significant, from incomplete recovery from re- lapses, secondary progressive disability worsening is not seen in neuromyelitis optica. Cases of neuromyelitis optica associated with anti-MOG antibodies have more frequent episodes of optic neuritis, and fewer of myelitis, with a better prognosis than anti- aquaporin 4 disease. Distinguishing neuromyelitis optica from multiple sclerosis is important because several drugs that are effective in the latter ei- ther exacerbate (interferon-β and natalizumab) or are ineffective (alemtuzumab) in neuromyelitis optica. Instead, acute treatment of neuromyelitis optica episodes involves corticosteroids and often plasma exchange, and maintenance therapy is with cortico- steroids and azathioprine or mycophenolate, with breakthrough disease leading to escalation to B-cell depletion (rituximab or ocrelizumab). Acute disseminated encephalomyelitis Typically, acute disseminated encephalomyelitis is a monophasic illness that develops within days or a few weeks after an infection or, more rarely, following vaccination. Formerly, it affected 1 in 1000 children with exanthematous illnesses, particularly measles and rubella, but these childhood illnesses, and hence their com- plications, are now less prevalent. A greater variety of causative organisms has been implicated in adult-onset acute disseminated encephalomyelitis, but in both groups a presumptive diagnosis often must be made in the absence of an identifiable preceding infection. Headache, drowsiness, meningeal irritation, signs of systemic infection, focal or generalized fits, and combinations of lesions indicating damage to the cerebrum, optic nerves, brainstem, or spinal cord evolve over the course of a few days. About 50% of cases occurring after Varicella infection present with a pure cerebellar syndrome. The cerebrospinal fluid contains a mixture of polymorphonuclear cells and lymphocytes with raised protein and a slight reduction in glucose; oligoclonal bands are usually not pre- sent. The key features of magnetic resonance imaging are that the lesions are all the same age (e.g. all enhancing at the same time) and no new lesions develop beyond the first four weeks of the illness. The individual lesions are usually more extensive and frequently involve the thalamic and basal ganglia grey matter, compared to multiple sclerosis. While there is an appreciable mortality, most patients sur- vive, sometimes with persistent neurological deficits. Table 24.10.2.3 Classification of neuromyelitis optica (NMO) spectrum disorder Classification Aquaporin 4 antibody result Number of required core clinical characteristics Positive At least one Negative At least two, of which one must be optic neuritis, myelitis, or area postrema syndrome Additional MRI requirements Core clinical characteristics Additional MRI requirements if AQP4 negative Optic neuritis Brain normal, involvement of > ½ optic nerve length Acute myelitis MRI lesion extending over 3 or more vertebral segments Area postrema syndrome (hiccups, vomiting) Dorsal medullary MRI lesion Acute brainstem syndrome Typical brainstem MRI lesion Symptomatic narcolepsy or diencephalic

syndrome Symptomatic cerebral syndrome with typical NMOSD brain lesions

24.10.2 Demyelinating disorders of the central nervous system 6039 The hyperacute form of acute disseminated encephalomyelitis (Hurst's disease) starts with headache and progresses over hours to disorientation, confusion, drowsiness, and coma. Events move quickly and the illness often proves fatal even before the diagnosis has been established. The combination of pyrexia and a marked cerebrospinal fluid pleocytosis with a predominantly neutro- phil response mimics pyogenic infection of the central nervous system, but the course is not influenced by antimicrobial treatment. Occasionally, the clinical and pathological features of acute haemor- rhagic leucoencephalitis are focal and suggest a rapidly expanding tumour or herpes simplex encephalitis. There is poor quality evidence to guide treatment of acute dis- seminated encephalomyelitis. Most important is appropriate supportive care, which often involves intensive care treatment. Monitoring of intracranial pressure can be helpful in severe cases, and decompressive hemispherectomy has been life-saving in a few individuals. For immunotherapy, early use of high-dose intravenous steroids is advised and, among those who do not respond to steroids, improvement is seen in 50% cases with plasmapheresis. There is little role for intravenous immunoglobulin. Acute disseminated encephalomyelitis does not recur. The entity of 'multiphasic disseminated encephalomyelitis' has not gained general acceptance. However, multiple sclerosis can rarely present with a similar picture, following which more typical epi- sodes of demyelination occur. Clues to this 'encephalopathic presentation' of multiple sclerosis are the presence, of cerebro- spinal fluid oligoclonal bands and MRI lesions of varying age, or new MRI lesions forming five or more weeks after the initial symptoms. Longitudinally extensive transverse myelitis Longitudinally extensive transverse myelitis is a feature of neuromyelitis optica, as described earlier. But it may also occur in isolation, often but not always with an antecedent infection, similar to acute disseminated encephalomyelitis in adults. Presentation is with pain at the site of the lesion, followed by weakness in the legs, sensory symptoms, and sphincter involvement. The weakness in- creases, and the clinical picture is that of spinal shock—features that are rarely seen in acute cord lesions due to multiple sclerosis. On imaging, the cord lesion usually extends over three vertebral segments. The spinal fluid shows an increased mononuclear cell count, numerically intermediate between the marked pleocy- tosis of acute necrotizing myelitis and the marginal abnormalities seen in multiple sclerosis; total protein is raised and oligoclonal bands may be present on electrophoresis, but the glucose is usu- ally normal. Transverse myelitis is more common in adults than children; there is a high frequency of persistent disability, but a much lower conversion to multiple sclerosis than following optic neuritis. Acute necrotizing myelitis causes rapidly progressive flaccid areflexic paraplegia with anaesthesia and loss of sphincter con- trol. The intensity of inflammation may result in severe pain with meningism, pyrexia, and systemic symptoms. The condition can mimic cord compression; and the cerebrospinal fluid changes often resemble pyogenic or tuberculous infection of the central nervous system. For these reasons, treatment with high-dose intravenous steroids, which may usefully influence mortality and limit long-term disability, is often withheld. Acute necrotizing myelitis has been described in association with herpes virus in- fection, and as a complication of acute lymphocytic leukaemia, lymphoma, carcinoma, and acquired immune deficiency syndrome. Relapsing optic neuritis Outside of multiple sclerosis, recurrent demyelinating inflamma- tory optic neuropathies occur with neuromyelitis optica, particu- larly those associated with anti-MOG antibodies. Chronic relapsing idiopathic neuropathy is a distinct entity with important treatment implications. People with this condi- tion typically have severe optic neuritis with considerable pain, which responds well to corticosteroids

but recurs on steroid with- drawal. MRI brain and cord scans (other than the optic nerves themselves) and cerebrospinal fluid are normal. This steroid- dependence marks it out from regular optic neuritis. Maintenance therapy with steroids and immunotherapy, such as mycophenolate or azathioprine, should be considered to prevent what is other- wise a poor visual outcome. Balo's concentric sclerosis The literature on this rare phenomenon is confusing. The pathognomic feature of Balo's lesions, seen pathologically and radiologically, are con- centric rings of demyelination separated by unaffected tissue. Such lesions may be seen alongside typical plaques in cases of multiple scler- osis, in which case it is best to think of them as one of the heterogenous pathological forms of multiple sclerosis lesion. However, some patients only present with Balo's lesions, which may be extensive and cause progressive lobar syndromes. The prog- nosis of these cases is very variable, from progressive deterioration causing a neurological death to spontaneous recovery. It is not even clear that this is a primary inflammatory disorder; some argue that the rings are a response to hypoxic injury with unaffected tissue pro- tected by 'hypoxic preconditioning'. Unsurprisingly, there is no clear treatment guidance. Harding's disease Patients with Leber's mitochondrial mutations may present with a syndrome that is identical to multiple sclerosis except that visual failure is more prominent. Curiously, this is more common in women, despite the fact that Leber's hereditary optic neuropathy is more common in men. Leber's mitochondrial mutations are not seen more commonly in cohorts of regular multiple sclerosis. There is no evidence to guide practice, but we recommend using standard disease-modifying therapies for multiple sclerosis. Noninflammatory demyelinating diseases Central pontine myelinolysis Central pontine myelinolysis seems to result from overzealous correction of a low (and occasionally also high) serum sodium. Demyelination correlates both with the degree of hyponatraemia and rate at which this is corrected; starting levels of less than 110 mmol/litre or rates of correction of more than 2 mmol/litre/h substantially increase the risk of central pontine myelinolysis. Rapid changes in sodium are better tolerated in acute than chronic

 hyponatraemia. The clinical context is usually hospital treatment of hyponatraemia, which may be due to liver disease, as a compli- cation of uraemia and haemodialysis, after prolonged vomiting or excess diuretic therapy. The illness affects central pontine pathways and spreads centri- fugally. The fully evolved clinical picture is of flaccid paralysis with facial and bulbar weakness, disordered eye movements, loss of balance, and altered consciousness. Extrapontine manifestations, including movement disorders and other features of extrapyramidal disease, may be seen. The clinical features are distinctive and present no diagnostic difficulties unless the reduction in serum sodium has been overlooked. Patients on intensive care may present with cen- tral pontine myelinolysis as a failure to wean from ventilation. The characteristic radiological changes may not appear for a few days after the clinical syndrome and often persist after clinical recovery. Prognosis depends on the underlying metabolic disorder. With sta- bilization of the serum sodium and management of bulbar failure, neurological recovery is usually complete, and the condition does not recur spontaneously. Toxic disseminated encephalomyelitis Rarely, a picture very similar to inflammatory disseminated enceph- alomyelitis can be induced by inhalation of cocaine or heroin vapour (from 'chasing the dragon'). Prognosis is variable. Inherited leucodystrophies The leucodystrophies are characterized by noninflammatory demye- lination. They include a heterogeneous group of conditions, often due to mutations affecting genes that determine the synthesis, main- tenance, and structure of myelin. Although rare even in paediatric practice, these need to be considered in young adults with atypical syndromes combining physical and intellectual deficits, sometimes with peripheral nerve

involvement, in whom imaging shows con- fluent lesions confined to white matter. The term diffuse cerebral sclerosis (Schilder's disease) was originally used to identify a mixed group of diseases affecting cerebral white matter and the term is now redundant. Adrenoleucodystrophy This important group of disorders is characterized by deposition of saturated fatty acids in the brain and other lipid-containing tissues as a result of defective very long chain fatty acyl-CoA synthetase activity in peroxisomes. Mutations are present in the ABC trans- porter gene. The molecular defect may result from failure of the adrenoleucodystrophy gene product to anchor very long chain fatty acids into the peroxisomal membrane or translocate these into per- oxisomes. Diagnosis can be made by serum analysis of very long chain fatty acids. Evidence of adrenal insufficiency is a valuable dis- criminator from multiple sclerosis. Pathological findings vary but may include inflammation; although considered reactive by most commentators, immunosuppression has been used in these condi- tions, to no useful effect. Four related syndromes share this biochemical abnormality: child- hood adrenoleucodystrophy and adult-onset adrenomyeloneuropathy are X-linked; neonatal adrenoleucodystrophy and Zellweger's syn- drome are autosomal recessive disorders. X-linked childhood adrenoleucodystrophy presents with behav- ioural disturbance, dementia, and epilepsy, followed by involvement of special senses and motor systems. Although a significant propor- tion of children later develop adrenal insufficiency, Addison's dis- ease may precede the neurological manifestations by several years. Treatment has been proposed with a dietary supplement containing a 4:1 mixture of glyceryl trioleate and trieructate, popularly known as Lorenzo's oil. This lowers the plasma levels of very long chain fatty acids, but does not appear to influence the phenotype in individ- uals with established neurological disease, although there may be a prophylactic role. Bone marrow transplantation may be successful in early symptomatic cases. Adrenomyeloneuropathy presents in young adult men with spastic paraparesis and sensory loss in the legs. Clues to the cor- rect diagnosis are an associated peripheral neuropathy or adrenal insufficiency. It may be associated with dementia later in the dis- ease course. Identification of the peroxisomal defect in easily sam- pled body tissues has led to the description of cases with obscure clinical manifestations; these include focal cerebral lesions, Kluver– Bucy syndrome, dementia, and spinocerebellar degeneration. Mild spastic paraparesis with sphincter involvement and peripheral neur- opathy may occur in obligate heterozygote female carriers with ele- vated very long chain fatty acids. Carriers tend not to have adrenal insufficiency, although abnormal brain MRI and delayed evoked po- tentials may be present. Autosomal recessive adrenoleucodystrophy and Zellweger's syn- drome present in infancy with seizures, hypotonia, retardation, ret- inal degeneration, and hepatic involvement. Metachromatic leucodystrophy Metachromatic leucodystrophy is an autosomal recessive lyso- somal storage disorder due to arylsulphatase A deficiency, leading to increased urinary sulphatide excretion with a deficiency of arylsulphatase A in urine, peripheral blood leucocytes and skin fibroblasts, or showing metachromatic material in peripheral nerve biopsies having segmental demyelination and remyelination. There is diffuse white matter involvement due to noninflammatory de- myelination with loss of oligodendrocytes, axon preservation, and reactive astrocytes which, together with macrophages, con- tain the metachromatic material, especially in the most extensively demyelinated areas. The clinical phenotype varies with the amount of surviving arylsulphatase A depending on heterozygosity of the mutant al- lele; pseudodeficiency refers to those individuals with low levels of arylsulphatase A that are sufficiently high not to display a clinical phenotype. Some affected individuals have a genetic defect of the arylsulphatase A activator and this is associated with a more com- plex pattern of sphingomyelin storage, biochemically and in terms of the tissue distribution. The most common form of metachromatic leucodystrophy de- velops in late infancy with delayed walking

due to the neuropathy, which may be painful. There are also features of brainstem involve- ment and the emergence of diffuse upper motor neurone signs with reduced intellectual development, optic atrophy, and death within

24.10.2 Demyelinating disorders of the central nervous system 6041 about five years from presentation. In later-onset childhood cases, after several years of normal development, there are behavioural changes with poor school performance, anticipating cerebellar and upper motor neurone disability, which then follows much the same course as in younger patients, although with less evidence for neur- opathy. The early adult form of metachromatic leucodystrophy is rare, or perhaps seldom diagnosed, and tends to present with in- tellectual or emotional abnormalities. Onset with dementia and behavioural disorders is usual with ataxia, paralysis, and optic at- rophy only developing at late stages; the presentation is occasion- ally with paraparesis or cerebellar ataxia and the condition can then more easily be mistaken for multiple sclerosis. Clinical evidence for peripheral neuropathy may be revealed by slowed nerve conduc- tion. Treatments have included dietary manipulation with reduced vitamin A and sulphur-containing substances, and bone marrow transplantation, but the successes are limited. Multiple sulphatase deficiency combines the features of meta- chromatic leucodystrophy with mucopolysaccharidosis. It also has neonatal, early childhood, and juvenile forms. The pattern of combined motor and mental regression or lack of development re- flecting widespread dysmyelination with peripheral neuropathy is associated with dysmorphic features and organomegaly. The more severe phenotype also reflects extensive neuronal loss due to the combination of stored sulphatide, sulphated steroids, and muco- polysaccharides. The enzyme defects are complex involving many sulphatases, including arylsulphatase A. Pelizaeus–Merzbacher disease The three phenotypes of X-linked Pelizaeus–Merzbacher disease usually present in childhood. The clinical features which may distin- guish the otherwise ubiquitous motor and developmental delay with epilepsy are abnormal eye movements, dystonia and choreoathetosis, and laryngeal paralysis. Affected individuals often stabilize with severe disabilities and live into early adult life. Some cases do not manifest until early adult life. MRI either fails to show myelin or de- picts myelin that is immature and with an atrophic brain. The molecular defect is most frequently due to duplication of a variable length of genome containing the proteolipid protein gene. Recent evidence implicates defects in the replication mechanism that leads to the complex rearrangements seen in Pelizaeus–Merzbacher disease. Proteolipid protein is normally involved in stabilizing the lamellar structure of central myelin. Gene dosage abnormalities re- sult in oligodendrocyte loss and failure of myelination. Krabbe’s disease Globoid cell leucodystrophy, an autosomal recessive condi- tion, usually presents as an early infantile disorder. The very rare late-onset form may be mistaken initially for multiple sclerosis. However, the disease usually progresses to include: progressive intellectual and motor deterioration, epilepsy, visual failure, and peripheral neuropathy leading to severe disabilities; pyrexia and other autonomic features usher in the onset of a vegetative state. Visual evoked potentials are delayed, and the spinal fluid has a raised protein level, but does not contain oligoclonal bands. MRI shows periventricular lesions subsequently extending into exten- sive white matter changes. The deficiency of α-galactocerebrosidase, best demonstrated in peripheral blood leucocytes or skin fibro- blasts, leads to the accumulation of galactocerebroside in oligo- dendrocytes and Schwann cells and characteristic myelin-laden macrophages or globoid cells. Adult-onset dominant leucodystrophies Forms of dominantly inherited leucodystrophy also occur - exclusively in adults and may closely resemble chronic progres- sive multiple sclerosis. MRI shows diffuse, nondiscrete, white matter disease, and there are no oligoclonal bands in the spinal fluid. It remains uncertain whether all the adult-onset dominant leucodystrophies are one and the same

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