24.15 The motor neuron diseases 6166 Tom Jenkins,

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ESSENTIALS The motor neuron diseases can be considered an extended family of conditions with pathology affecting the lower and/or upper motor neurons, leading to clinical features of limb and/or bulbar weakness. Accurate diagnosis is essential to guide management, in particular, treatment options, any genetic implications, and prognosis. Amyotrophic lateral sclerosis is the family prototype and is a dif- fuse neurodegenerative disorder characterized by both upper and lower motor neuron cell death, causing progressive paralysis of limb, bulbar (speech and swallowing) and respiratory muscles, and re- sulting in death from respiratory failure. The cardinal clinical feature of combined upper and lower motor neuron signs in various body regions (bulbar, arms, trunk, legs) forms the basis for diagnostic cri- teria. There is no cure and the disease progresses relentlessly, with few patients surviving beyond 5 years from symptom onset. Several rarer motor neuron diseases affect either lower or upper
motor neurons exclusively. The lower motor neuron syndromes include progressive muscular atrophy (a pure lower motor neuron variant of amyotrophic lateral sclerosis), various inherited spinal muscular atrophies, Kennedy’s disease (X-linked recessive bulbospinal neuronopathy), Hirayama disease and, importantly, multifocal motor neuropathy with conduction block, which is treatable with intravenous immunoglobulin therapy. Upper motor neuron syndromes are the rarest forms of motor neuron disease and include primary lateral sclerosis (a pure upper motor neuron variant of amyotrophic lateral sclerosis), hereditary spastic para- paresis, and, especially in the developing world, the dietary spastic parapareses lathyrism and konzo. Diagnosis of motor neuron diseases is clinical, supported by
electrophysiological examination and, in the case of amyotrophic lateral sclerosis, exclusion of

mimics. Age of onset, family history, and rate of deterioration are important diagnostic clues. While most motor neuron diseases are incurable, many of the symptoms are treatable and optimally managed in a multidisciplinary clinic setting. In amyotrophic lateral sclerosis, recent discoveries, such as insights into TDP-43 pathology and the identification of the C9orf72 gene are helping decipher the incompletely understood pathogenesis, leading to prospects of better therapies in the future. Introduction Motor neuron diseases result from death and dysfunction of lower motor neurons in the anterior horns of the spinal cord and brainstem and/or upper motor neurons in the cerebral cortex and descending corticospinal tracts, leading to weakness of voluntary muscles in the bulbar region, limbs, and trunk. Clinical signs of lower motor neuron involvement are muscle wasting, fasciculation, and flaccid weakness; upper motor neuron dysfunction produces spasticity, clonus, hyperreflexia, extensor plantar responses, and a pyramidal pattern of weakness. The nomenclature can be confusing; the term ‘motor neuron dis- eases’ describes a family of related disorders within which there is an extensive differential diagnosis (Table 24.15.1), as outlined in this chapter. In the United Kingdom, the term ‘motor neuron dis- ease (MND)’ is used as an umbrella term to describe collectively amyotrophic lateral sclerosis (ALS) (with clinical evidence of both upper motor neuron (UMN) and lower motor neuron (LMN) in- volvement) and its rarer variants, progressive muscular atrophy, and primary lateral sclerosis. In the United States, the term ALS, or sometimes Lou Gehrig’s disease, often refers to motor neuron disease in general (i.e. encompassing ALS, progressive muscular at- rophy, and primary lateral sclerosis). In this chapter, we will use the UK term ‘MND’ to refer to the prototypical motor neuron disorder encompassing ALS, progressive muscular atrophy, and primary lat- eral sclerosis. Progressive bulbar palsy is used variably to refer to a subgroup of patients with MND with isolated bulbar symptoms, usually of pure LMN phenotype. Pseudobulbar palsy describes UMN bulbar weakness, often associated with emotional lability; it is seen in primary lateral sclerosis, ALS, and other conditions and does not imply a specific aetiology. Monomelic amyotrophy refers to a clinical syndrome of LMN arm weakness; aetiology should not be implied by this term, but it has been used interchangeably to refer to both Hirayama disease (discussed next) and ‘flail arm’ MND in the literature. ‘Flail leg’ MND is also described, a LMN- predominant syndrome restricted to the legs, and is also referred to as ‘pseudopolyneuritic variant’ in older literature. Diagnosis of the motor neuron diseases is predominantly clin- ical, and centred on the identification of upper and/or lower motor neuron signs in various body regions. Electrophysiology is the 24.15 The motor neuron diseases Tom Jenkins, Alice Brockington, and Pamela J. Shaw

 most important supportive investigation; electromyography can be used to identify subclinical LMN involvement in MND (and contributes to diagnostic criteria), or to identify conduction block in demyelinating motor neuropathies, such as multifocal motor neuropathy with conduction block. Genetic testing is available for Kennedy’s disease, some forms of spinal muscular atrophy, her- editary spastic paraparesis, and familial MND. Motor neuron dis- eases are generally incurable but symptomatic treatment for many clinical features is available. Respiratory muscle weakness can now be treated with noninvasive intermittent positive pressure ventila- tion and has been shown to improve survival and quality of life in MND. In diseases with bulbar features, malnutrition can be treated by feeding via nasogastric or gastrostomy tube. Spasticity can be managed with baclofen, tizanidine, gabapentin, diazepam, or dantrolene, while walking aids, wheelchairs and arm supports can address inadequate limb function. Electronic communication de- vices have advanced significantly, and eye tracking software is now available for those with advanced disease. Citalopram, amitrip- tyline, and dextromethorphan/quinidine may

help with emotional lability, often a feature in patients with pseudobulbar palsy. Housing and workplace modifications can allow patients to maintain inde- pendence despite worsening disability. The motor neuron diseases, particularly MND, are a focus of in- tensive neuroscience research. Therapeutic discoveries from animal models and clinical research raise the prospect for new treatments in the foreseeable future. Table 24.15.1 Classification of the motor neuron diseases Disease Clinical features Aetiology Amyotrophic lateral sclerosis and its variants (collectively MND) Amyotrophic lateral sclerosis (ALS) UMN and LMN disease affecting limbs, trunk, and bulbar muscles 90–95% sporadic; 5–10% familial, usually AD: Causative genes include C9ORF72, SOD1, TDP43, FUS (and rarely, VAPB, DNCT1, ANG, CHMP2B, VCP, Alsin, SETX plus others outlined in Table 24.15.2) Progressive muscular atrophy (PMA) Pure LMN variant of ALS Primary lateral sclerosis (PLS) Pure UMN variant of ALS ALS–FTD ALS associated with frontotemporal dementia Lower motor neuron syndromes Autosomal recessive spinal muscular atrophy (SMA) Proximal weakness with variable age of onset. Type I (Werdnig–Hoffman) presents in infancy, type II (intermediate) in early childhood, type III (Kugelberg–Welander) in late childhood, type IV: is adult onset AR inheritance due to mutations in SMN1 gene. Variable levels of expression of a similar gene (SMN2) influence age of onset and clinical severity Autosomal dominant SMA Rare adult-onset proximal SMA with AD inheritance in a few Brazilian families AD inheritance due to mutations in the VAPB gene (this gene can also rarely cause typical and atypical ALS) Acute infantile SMA without SMN mutations Resembles SMN-related disease, but with additional features (e.g. arthrogryphosis, contractures) Causative genes unknown Distal SMAs Group of disorders comprising distal weakness with diverse patterns of muscle involvement (e.g. upper limb predominant, lower limb predominant, scapuloperoneal, vocal cord paralysis) Genetically diverse: causative genes identified are GARS, BSCL2, IGHMBP2, HSP22, HSP27 X-linked spinobulbar muscular atrophy (Kennedy’s disease) Slowly progressive LMN disease affecting limbs and bulbar muscles, usually in men, associated with gynaecomastia, testicular atrophy, and diabetes X-linked inheritance, due to triplet repeat expansion of the androgen receptor gene Hereditary bulbar palsy of infancy and childhood Brown–Vialetto–van Laere syndrome is a progressive pontobulbar palsy with deafness; Fazio–Londe syndrome is part of the same disease spectrum, without deafness AR disease due to mutations in C20ORF54, a homologue of the rat riboflavin transporter gene Hirayama disease Weakness and wasting of one or both arms (rarely legs reported too), usually affecting young men, without generalized weakness Sporadic, may be acquired Post-polio syndrome Delayed progressive weakness in a limb previously affected by poliomyelitis Acquired Multifocal motor neuropathy with conduction block Multifocal slowly progressive muscle weakness, with minimal wasting, and conduction block on electrophysiology which responds to intravenous immunoglobulin Immune-mediated acquired Upper motor neuron syndromes Hereditary spastic paraparesis Slowly progressive spastic paraparesis that may be pure, or complicated by other neurological features, such as epilepsy, dementia, amyotrophy, or peripheral neuropathy Genetically diverse; usually AD inheritance, but may be AR or X-linked. Spastin mutations account for 40% of cases Dietary spastic parapareses Lathyrism and konzo are spastic parapareses caused respectively by consumption of chickling peas, and unprocessed cassava Acquired AD, autosomal dominant; ALS, amyotrophic lateral sclerosis; ANG, angiogenin; AR, autosomal recessive; BSCL2, Berardinelli–Seip congenital lipodystrophy 2; CHMP2B, charged multivesicular body protein 2b; DNCT1, dynactin; FTD, frontotemporal dementia; FUS, fused in sarcoma; GARS, glycyl tRNA synthetase; HSP, heat shock protein; IGHMBP2, immunoglobulin mu-binding protein 2; LMN, lower motor neuron; ORF, open reading frame; PLS, primary lateral sclerosis; PMA, progressive muscular atrophy; SETX, senataxin; SMA, spinal muscular atrophy; SMN, survival motor neuron; SOD1, superoxide dismutase 1; TDP43,

TAR DNA binding protein-43; UMN, upper motor neuron; VAPB, vesicle-associated membrane protein-associated protein B; VCP, valosin-containing protein.

section 24 Neurological disorders 6168 Amyotrophic lateral sclerosis ALS occurs worldwide, with an incidence of approximately 2/100 000 population and a prevalence of 6/100 000. It is more common in men and the incidence increases with advancing age, peaking at 64–74 years. A family history of ALS is present in 5–10% of pa- tients, with an autosomal dominant inheritance pattern in most fa- milial cases. Although familial disease presents on average a decade earlier, in individuals, it is indistinguishable clinically from sporadic ALS. There have been major recent advances in the understanding of the genetic basis of familial ALS (Table 24.15.2). The discovery of in- tronic hexanucleotide (GGGGCC) expansions in the C9ORF72 gene is of major significance as it accounts for up to 50% of cases of fa- milial ALS and approximately 7% of apparently sporadic cases (10% of ALS as a whole), by far the most prevalent gene to date, and has Table 24.15.2 Genetic subtypes of amyotrophic lateral sclerosis Common causes of adult-onset autosomal dominant ALS Mutation Chromosome C9ORF72 Hexanucleotide repeat as an intronic expansion in chromosome 9 open reading frame 72 9p Discovered in 2011, and accounts for 40–50% of familial cases. Patients with C9ORF72-related ALS have a higher prevalence of frontotemporal dementia and the genotype also causes frontotemporal dementia without ALS. The function of this gene is currently unknown, though the encoded protein has been shown to be involved in the initiation of autophagy. SOD1 Missense mutations in Cu/Zn superoxide dismutase 1 21q Discovered in 1993, and accounts for 20% of familial cases. SOD1 catalyses conversion of toxic superoxide anion radicals to hydrogen peroxide. SOD1 mutations damage cells by toxic gain of function with dysregulation of multiple cellular processes. The well-characterized SOD1 mouse model has enhanced understanding of ALS, but SOD1 ALS has important differences to sporadic disease and most other familial forms, notably the absence of TDP-43 cytoplasmic inclusions. TDP43 Missense mutations in TAR DNA binding protein-43 1p Discovered in 2008, and accounts for about 3–5% of familial cases. TDP43 is involved in multiple elements of RNA processing. FUS Missense mutations in fused in sarcoma 16q Discovered in 2009, and accounts for about 3% of familial cases. FUS also plays a role in RNA processing. Rare genetic causes of adult-onset ALS • Mutations in the vesicle trafficking protein VAPB have been described in phenotypically variable ALS in Brazilian families. • The motor protein DCTN1 has shown mutations in a family with a lower motor neuron disease with vocal cord paralysis, and in some patients with ALS and frontotemporal dementia. • ANG is a hypoxia-response protein that stimulates angiogenesis. Mutations in the ANG gene have been demonstrated in patients with ALS, largely with Scottish or Irish ancestry. • CHMP2B is a vesicle sorting protein originally identified in patients with frontotemporal dementia, and subsequently found in patients with ALS without dementia, who had a predominantly LMN phenotype. • VCP mutations were originally described in families with an unusual disorder—inclusion body myopathy with early-onset Paget’s disease and frontotemporal dementia—and have recently been identified in an exome sequencing study, in 1–2% of cases of familial ALS. • OPTN1, a causative gene in primary open angle glaucoma, interacts with NFKB. Two homozygous mutations in OPTN1 have been described in consanguineous families with ALS in Japan, and a third heterozygous mutation subsequently identified in nonconsanguineous Japanese families with ALS. It has also rarely been identified in patients of European descent. • UBQLN2 mutations were identified in a large pedigree with an X-linked dominant pattern of inheritance of ALS, and also in four further families. • SQSTM1 (p62) mutations were identified in 15 patients with familial and sporadic ALS, in a candidate gene screening study of 546 ALS patients. These variants were not found in normal controls, but linkage

with the disease was not established. • FIG4 Screening of FALS and SALS cases initially identified nine variants, with six showing impaired function in yeast models. • ATXN2 Intermediate CAG repeats of 27–33 in this gene show a strong association with MND. • SIGMAR1 Using homozygosity mapping, a missense mutation in this gene was found to cause autosomal recessive MND in a large consanguineous family. • PFN1 Exome sequencing initially identified two multigenerational families with mutations in this gene and further rare cases have subsequently been identified. • MATR3 Mutations in this gene which encodes an RNA/DNA binding protein have been identifies in a few families with MND. • TUBA4A Exome sequencing has identified mutations in several families with ALS/MND. Mutations lead to disrupted microtubule assembly and stability. • CHCHD10 Exome sequencing initially identified a mutation in a family with MND, FTD, ataxia, and myopathy. Subsequently several mutations were identified in FALS cases. The encoded protein localizes to mitochondria, but its function is unknown. • TBK1 encodes a protein which has a role in innate immunity, autophagy, and NFKB signalling. Mutations have been found in families with ALS, ALS–FTD, and FTD. • ERBB4 Rare mutations have been described in Japanese and Canadian families. • hnRNPA1 A mutation has been identified in a single FALS case. Rare genetic causes of juvenile-onset ALS • Slowly progressive juvenile-onset ALS is inherited in a recessive manner in a few large consanguinous families in Northern Africa and the Middle East. Some of these cases are due to mutations in Alsin, a putative GTPase regulator. • A rare autosomal dominant juvenile-onset ALS with slowly progressive amyotrophy and pyramidal signs is caused by missense mutations in SETX, a DNA/RNA helicase. • SPG11 Mutations in spatacsin are a known cause of hereditary spastic paraparesis. Several families with autosomal recessive juvenile-onset ALS have been identified with mutations in this gene. ALS, amyotrophic lateral sclerosis; ANG, angiogenin; ATXN2, ataxin 2; CAG, cytosine–adenine–guanine; CHCDHD10, coiled-coil helix coiled-coil helix domain containing protein 10; CHMP2B, charged multivesicular body protein 2b; DNCT1, dynactin; ERBB4, erb-b2 receptor tyrosine kinase 4; FIG4, phosphoinositide 5-phosphatase; FUS, fused in sarcoma; hnRNPA1, heterogeneous nuclear ribonuclear protein A1; LMN, lower motor neuron; MATR3, matrin 3; NFKB, nuclear factor kappa β; OPTN, optineurin; ORF, open reading frame; PFN1, profiling 1; SALS, sporadic amyotrophic lateral sclerosis; SETX, senataxin; SOD1, superoxide dismutase 1; SIGMAR1, sigma nonopioid intracellular receptor 1; SPG11, spastic paraplegia gene 11, spatacsin; SQSTM, sequestosome; TBK1, TANK-binding kinase; TDP43, TAR DNA binding protein-43; TUBA4A, tubulin-α 4 A; UBQLN, ubiquilin; VAPB V, vesicle- associated membrane protein-associated protein B; VCP, valosin-containing protein.

24.15 The motor neuron diseases 6169 sparked intense research into the normal function of the gene, as a po- tential clue to pathophysiology. The C9ORF72 mutation can also cause frontotemporal dementia (FTD), highlighting pathophysiological overlap between the two conditions. Genetic testing for C9ORF72, TDP-43, FUS, and SOD1 mutations, which together account for ap- proximately 70% of familial cases of ALS, is now available in the clin- ical setting. The cause of ALS in the remainder of apparently sporadic cases is largely unknown. Several pathogenic processes have been im- plicated. The discovery of C9ORF72 suggests that genetic factors may play an important role even in apparently sporadic disease, and the pre- vious discovery of mutations in the ribonucleic acid (RNA) processing genes TDP43 and FUS in patients with familial ALS has focused at- tention on the importance of RNA splicing and processing to motor neuron survival. Motor neurons are large cells with high metabolic requirements, and mitochondrial dysfunction and oxidative stress are likely to be involved in their susceptibility to degeneration. They have numerous glutamatergic inputs, and are therefore vulnerable to excitotoxicity. Riluzole,

the only effective disease-modifying drug in ALS, has antiglutamate effects, supporting this hypothesis. Motor neurons have the longest axons of any human cell and some evidence suggests that the disease process begins at the distal axon, perhaps due to perturbed axonal transport and disruption of the cytoskeleton. Intracellular protein aggregation is a notable pathological feature of the disease, although it is not known whether this is damaging to the cell. A major component of the aggregated protein within motor neurons is TDP-43 (except in SOD1 cases), which becomes mislocalized from its normal nuclear location into the cytoplasm. There has also been recent interest in the role of the interactions between motor neurons and glial cells and inflammatory events in the pathogenesis of the disease. Epidemiological studies designed to determine the effect of occupational exposures and lifestyle factors on the risk of developing ALS have often given inconsistent results. Cigarette smoking has been associated with a significantly increased risk of ALS. Many high- profile sportsmen have been afflicted by ALS, most notably the base- ball player Lou Gehrig, and most clinicians would recognize the slim, sporty phenotype of the ‘typical’ patient. There is increasing evidence from case-control studies to support physical activity as a risk factor in susceptible individuals, but further population-based studies are needed, and it remains unclear whether any associations are causative or co-occur with an as-yet uncharacterized risk profile. The current in- complete understanding of ALS pathophysiology represents the main barrier to developing effective treatment and is the focus of intense re- search interest worldwide. Pathology Lower motor neurons degenerate in clinically affected areas of the spinal cord and brain stem, and associated diffuse astrocytic gliosis occurs. Surviving neurons show intracellular inclusion bodies; ubiquitinated inclusions within which the mislocalized protein TDP-43 is a major component are the most frequent and specific (Fig. 24.15.1). Other inclusion bodies, such as eosinophilic Bunina bodies and accumulations of neurofilaments, are also seen. Axonal loss and gliosis in the descending motor pathways gives rise to the lateral sclerosis, most prominent in the medulla and cervical spinal cord, which gives the disease its name. Changes in motor cortex are more variable, but, in cases with severe UMN involvement, Betz cells are depleted. There is relative sparing of Onuf’s nucleus in the sacral spinal cord, and the brainstem oculomotor nuclei, which explains why sphincter dysfunction and ophthalmoparesis, respectively, are not generally observed clinical features. It is now recognized that (a) (b) (c) Fig. 24.15.1 TDP43 immunostaining of the anterior horn of the spinal cord. (a) Normal motor neuron where TDP- 43 staining is predominantly in the nucleus. (b) Pathological motor neuron in a case of motor neuron disease. There is depletion of TDP-43 from the nucleus and aggregation as a compact inclusion in the cytoplasm of the cell. (c) Skein-like TDP-43 inclusion in the cytoplasm of a spinal motor neuron from a case of motor neuron disease.

section 24 Neurological disorders 6170 other populations of neurons can also degenerate in motor neuron disease even though this is not usually evident clinically. For example, changes in the cerebellum, basal ganglia and sensory areas have been identified in imaging studies and abnormalities of central and per- ipheral sensory pathways described in electrophysiological studies. However, for practical purposes of clinical diagnosis at least early on, ALS can still be considered a motor syndrome, sometimes with asso- ciated cognitive manifestations; up to 10% of patients develop overt frontotemporal dementia. More subtle cognitive impairment is evi- dent on detailed neuropsychological testing in a much higher pro- portion of patients. In the few patients who are treated with invasive ventilation after the onset of respiratory failure, the disease may be prolonged by many years and, in these patients, the ‘total manifest- ations’ of ALS are seen, with widespread pathological changes, dif- fuse cerebral atrophy, EEG slowing, and the end-stage of a

locked-in syndrome. The lesson from these patients is that ALS is a generalized neurodegenerative disorder, in which the motor neurons are particu- larly vulnerable. A subgroup of patients with isolated frontotemporal dementia (FTD), without motor neuron degeneration, also demon- strate cortical ubiquitin-only neuropathology (FTD-U). The idea that this reflects a shared pathogenesis is supported by the identi- fication of mutations in several genes (in particular C9ORF72; also TDP43, CHMP2B, DCN1, VCP) in families with cosegregation of ALS and FTD. Pure ALS, ALS with cognitive impairment, ALS–FTD, and pure FTD may therefore represent a continuous spectrum of ubiquitin-associated neurodegenerative disease. Clinical features ALS typically begins focally, but then spreads to contiguous regions ‘like a bush fire’. Patients tend to present with symptoms in a single body region, bulbar, arm or leg in approximate thirds and respiratory in approximately 1%. With time, the disease usually generalizes and symptoms in multiple regions become apparent. The Awaji Shima and El Escorial research diagnostic criteria for ALS require evidence of both UMN and LMN signs in three of the four body regions for a definite diagnosis, with less extensive involvement categorized as probable or possible ALS. In routine clinical practice, most diagnoses are made at these earlier, incomplete stages. The spinal forms of ALS usually present with weakness of one limb, often evident as intrinsic hand muscle weakness or foot drop (Figs. 24.15.2 and 24.15.3). Asymptomatic involvement of other limbs, especially fascicula- tions, is often evident on examination. Wasted, fasciculating muscles with brisk or even retained reflexes are an ominous finding, espe- cially if present in the bulbar region or more than one body region. With progressive disease, patients become wheelchair or bed-bound, or unable to use their arms for activities of daily living. Despite en- forced recumbency, curiously, pressure sores are relatively unusual. Bulbar involvement leads to weakness of the tongue, pharynx, and larynx and results in dysarthria, which almost invariably precedes dysphagia, with risk of aspiration pneumonia (Fig. 24.15.4). The tongue may exhibit LMN features of bulbar palsy (wasting, weak- ness, and fasciculations), UMN features of pseudobulbar palsy (spasticity, immobility with ‘hot potato’ speech, and a brisk jaw jerk)
Fig. 24.15.3 Wasting of the lower limbs in a patient with amyotrophic lateral sclerosis. Involvement of tibialis anterior causing footdrop is typical. Fig. 24.15.4 Appearance of the tongue in a patient with bulbar-onset amyotrophic lateral sclerosis. The tongue is wasted and spastic (this is the maximal extent of protrusion). Fig. 24.15.2 Wasting of the hands in a patient with amyotrophic lateral sclerosis. Prominent involvement of the first dorsal interosseus muscle is typical.

 or both. The presence of pseudobulbar palsy is associated with ‘emo- tional incontinence’; evidence of uncontrollable crying or laughter may be evident in clinic and is generally distinguishable as different from the understandable upset relating to diagnosis. Palatal move- ments are reduced. There may be weakness of neck extensors leading to ‘head-drop’ and mild facial weakness. With progression of bulbar disease, patients may become anarthric. Some people choose tube feeding to prevent an intolerable situation of hunger that cannot be alleviated due to inadequate bulbar function. The cough becomes weak because of vocal cord paresis and weakness of expiratory muscles and this further increases aspiration risk. Weight loss is a common feature, can partly be attributed to bulbar dysfunction and muscle loss but also appears to reflect a direct hypermetabolic effect of the disease process. Weakness of the diaphragm and intercostal muscles almost invariably develops as the disease progresses. With the onset of respiratory failure, patients may complain of dyspnoea or orthopnoea, but more subtle symptoms are often earlier mani- festations, such as fragmented sleep, daytime somnolence, anorexia, and morning headaches due to nocturnal carbon dioxide retention. These symptoms may not be volunteered by patients and should be specifically sought, as they are treatable with

noninvasive ventila- tion. However, eventually respiratory failure worsens and is the usual mode of death, at a median of 2–3 years from first symptom onset. Clinical variants Although combined upper and lower motor neuron degeneration is the hallmark of classical ALS, a pure LMN variant—progressive mus- cular atrophy—and a pure UMN variant—primary lateral sclerosis— are considered part of the same disease spectrum (i.e. MND) because they all demonstrate ubiquitinated pathology at autopsy. With disease progression, many of these patients will acquire clinical features of classical ALS. Patients that retain a pure LMN or, especially, UMN phenotype have a favourable prognosis compared with ALS. Prognosis ALS progresses relentlessly and is invariably fatal. Death com- monly results from ventilatory respiratory failure or aspiration pneumonia. Weight loss and malnutrition confer a worse prog- nosis. Median survival from first symptom onset in bulbar-onset disease is 20 months and, in limb-onset disease, 29 months. Fifteen per cent (15%) of patients with limb-onset disease survive longer than 5 years. Occasional patients survive much longer. Prolonged survival is more unusual in bulbar-onset disease. Differential diagnosis and investigation The diagnosis of ALS is usually evident on clinical grounds at presentation, which is often delayed, due to the insidious nature of onset. Electrophysiology is performed to confirm active and chronic denervation in multiple regions and to exclude poten- tially treatable mimics, such as demyelinating neuropathy, myop- athy, or myaesthenia gravis (the latter especially in patients with bulbar onset). Cranial and cervical imaging may be used to exclude structural brainstem pathology or coexistent myeloradiculopathy causing mixed UMN and LMN signs, but these are infrequently viable differential diagnoses in practice. We have seen patients with both tongue and laryngeal carcinoma masquerading as bulbar-onset MND; such differentials can be identified on imaging but there are usually additional clinical clues. Sometimes UMN involvement is not clinically demonstrable; for example, patients may have ab- sent Babinski’s responses due to severely denervated toe extensor muscles. In these circumstances, diagnosis is more challenging, and generally patients with pure UMN or LMN syndromes require more extensive investigation. Unfortunately, electrophysiological central motor conduction studies are a less reliable marker of UMN in- volvement in such cases than had been anticipated, but assessment of cortical hyperexcitability on specialized transcranial magnetic stimulation protocols (Short Interval intraCortical Inhibition, SICI) shows promise. The usual diagnostic problem lies in differentiating ALS from other motor neuron diseases, In addition to pure LMN or UMN phenotype, other red flags for alternative diagnoses include a young age of onset, unusually slow progression, parental consan- guinity, or dysphagia preceding dysarthria. Fasciculations can be normal in athletes and benign cramp- fasciculation syndromes without evidence of weakness or de- nervation, usually affecting middle-aged adults, do not evolve into motor neuron disease. It is usual to exclude hyperthyroidism, hypercalcaemia, and other metabolic derangements that can cause fasciculations in the work-up of ALS. Multifocal motor neuropathy is an important differential of progressive muscular atrophy because it is treatable. There may be marked weakness but little wasting, pre- dominantly affecting the arms. Proximal conduction block can be difficult to identify on electrophysiology and lumbar puncture and a trial of intravenous immunoglobulin may be warranted in suspected cases. Kennedy’s disease, occurring in males is much more slowly progressive than ALS and causes a pure LMN syndrome, often asso- ciated with gynaecomastia. Chin fasciculations can be a clue. Genetic analysis of the androgen receptor gene should be performed in sus- pected cases. Inclusion body myositis can present with wasting and weakness, which is usually more symmetrical than in ALS. Finger flexors are often weak (in contrast they are often relatively spared in ALS) and creatine kinase (CK) levels may be elevated (although modest elevation in CK up to 1000 IU/litre is not uncommon in ALS due to denervation). ALS as a

paraneoplastic syndrome is highly controversial. Hexosaminidase deficiency (autosomal recessive GM2 gangliosidosis) can present a variable neurological picture, oc- casionally as a motor syndrome with LMN and, rarely, also UMN involvement. More commonly, there are additional features such as cerebellar ataxia or dementia. Hexosaminidase assays should be re- served for young and/or atypical patients, particularly in those of Ashkenazi Jewish extraction. Giving the diagnosis Time is required because the news is devastating and patients and their families often have many difficult questions. A skilled clinician will convey the necessary hard truths about implications and prog- nosis while providing support and maintaining hope. Ongoing and active support following diagnosis is very important, and can be most effectively provided in specialist centres by a multidisciplinary team. Patients may also benefit from contact with specialist char- ities, such as the Motor Neurone Disease Association (MNDA) in the United Kingdom. Treatment Disease-modifying therapy There is no cure for ALS. Riluzole, an antiglutamatergic agent, re- mains the only conclusively proven disease-modifying therapy.

section 24 Neurological disorders 6172 Pooled analysis of the four trials, including 974 riluzole-treated pa- tients and 503 placebo-treated patients, showed that 50 mg twice a day increased median survival from 11.8 to 14.8 months ($p = 0.046$). There were small beneficial effects on both bulbar and limb func- tion, but not on muscle strength. Riluzole is generally well tolerated by patients; nausea, gastrointestinal upset, and raised transaminase enzyme levels may occur but are often transient and self-limiting. Clinical trials of many different agents including branched-chain amino acids, dextromethorphan, total lymphoid irradiation, the free radical scavenger acetylcysteine, gabapentin, creatine, vitamin E, lithium, coenzyme Q10, olesoxime, pentoxyfilline, glatiramer acetate, dexpramipexole have all proven negative to date. Edaravone, a free radical scavenger, is approved in Japan and the USA, based on a small reduction in rate of deterioration of ALS functional rating scale scores in a selected patient sub-group. There was no effect on survival and the medication is not currently licensed for use in Europe. Symptomatic therapy In contrast to the limited disease-modifying therapeutic options, much can be done to address symptoms, disability, and distress. A multidisciplinary setting appears to improve survival in obser- vational studies and usually includes a neurologist, specialist nurse, respiratory, anaesthetic and gastroenterology expertise (for nonin- vasive ventilation and gastrostomy insertion), speech and language therapist, physiotherapist, occupational therapist, social worker, and links to palliative care medicine. Charities, such as the Motor Neuron Disease Association in the United Kingdom, are often able to facilitate equipment provision. Respiratory function can be monitored clin- ically, and through forced/slow vital capacity, noninvasive random capnography and capillary blood gases, and augmented by over- night oximetry and capnometry when necessary. Noninvasive ven- tilation (NIV), usually delivered overnight initially, has been shown to prolong survival by a median of 205 days, and to improve quality of life in ALS, at least in patients without severe bulbar dysfunction. Diaphragm pacing was evaluated in a recent clinical trial but proved inferior to NIV. Cough assist devices are used to help clear respiratory secretions, and have hypothetical advantages in preventing aspiration pneumonia; a clinical trial is required to assess whether there is any survival benefit. Decisions about invasive ventilation pose complex practical and ethical dilemmas. Many patients prefer, and many clin- icians advise, to avoid endotracheal intubation in a disease causing such widespread and irreversible weakness, as a locked-in syndrome is the end result. At earlier stages of disease, secretion management is important. Excess salivation can be a significant problem, especially for patients with bulbar disease, and can be effectively treated using anticholinergics, such as hyoscine patches, sublingual atropine drops, glycopyrronium,

amitriptyline tablets, or botulinum toxin injection to the salivary glands. Carbocisteine is used to thin viscous secre- tions and facilitate expectoration. Early swallowing problems may be addressed by simple measures such as a chin tuck, attention to food consistency, and nutritional supplements. Later, more severe dysphagia can be treated with a gastrostomy tube inserted either under endoscopic or radiological guidance. Some centres now per- form a hybrid technique, which allows a larger diameter, more secure tube to be placed without conscious sedation, and in the presence of noninvasive ventilation, an important consideration as gastrostomy insertion becomes more risky with respiratory weakness, especially when forced vital capacity falls below 50%. Patients and clinicians may consider gastrostomy in the presence of significant weight loss, recurrent aspiration pneumonia, or when frequent choking or dys- phagia makes mealtimes prolonged or intolerable. Gastrostomy tube insertion has been shown to stabilize weight in ALS; while weight loss is an adverse prognostic factor, any survival and quality of life bene- fits remain to be determined in trials. The aims are to avoid a hungry, dysphagic patient unable to fulfil their nutritional requirements and to facilitate discharge home. Speech failure can be treated using a Lightwriter device in patients with adequate hand function, or by computer-assisted communication devices operated through pres- sure, blowing, head nodding, blinking or eye tracking, depending on an individual's capabilities. Lower motor neuron syndromes These forms of motor neuron disease generally follow a more benign course than ALS. Young age of onset and positive family history may suggest an inherited disorder. The pattern of weakness can also help differentiation. Progressive muscular atrophy The progressive muscular atrophy variant represents 5–10% of MND. A proportion of these patients will develop UMN signs later in the disease course, and are then referred to as LMN-predominant ALS. Patients with pure progressive muscular atrophy tend to have longer survival than those with classical ALS. The absence of UMN signs should prompt consideration of other motor neuron diseases, such as multifocal neuropathy with conduction block, spinal mus- cular atrophy, Hirayama disease or Kennedy's disease. Multifocal motor neuropathy with conduction block Patients may present at any stage of adult life with multifocal and slowly progressive muscle weakness over as much as 20 years. The clinical picture is immensely variable. Distal limb muscles are mainly involved, often notably asymmetrically. The first symptoms and most severe weakness usually affect the arms. A third present with drop of an individual finger. Characteristically, severely weakened muscles show little or no wasting. Reflex loss is generally restricted to markedly affected muscles. The condition is neurophysiologically heterogeneous, ranging from isolated muscle denervation changes on electromyography through classical multifocal conduction block in motor nerves on nerve conduction studies, and occasionally a dif- fuse demyelinating, pure, motor peripheral neuropathy. There may be no electrophysiological abnormality in early cases or if conduc- tion block is proximal. Serum antibodies to GM1 gangliosides are detectable in one-third of cases, but are of no proven pathogenic sig- nificance, and lack specificity for the condition (these antibodies can be seen in ALS too). The condition progresses insidiously, sometimes in a stepwise manner. Spontaneous remissions occur only occasion- ally, and usually in the subacute subgroup. High-dose intravenous human immunoglobulin (IvIg) therapy can produce dramatic im- provement lasting 6–8 weeks and repeat administration is the main- stay of treatment in symptomatic patients. With IvIg administered sufficiently regularly to prevent end-of-dose deterioration, pro- gressive motor axonal loss can be largely or completely prevented. Steroid therapy does not improve multifocal motor neuropathy, and may precipitate further deterioration.

24.15 The motor neuron diseases 6173 Spinal muscular atrophy Classical spinal muscular atrophy comprises a group of autosomal recessive inherited LMN degenerative disorders that affect prox- imal muscles, and are associated with deletions at 5q13 of the SMN1 survival motor neuron gene. The precise role of SMN has not been elucidated, but ribonucleoprotein or gene-splicing regulation is a likely function. Type I acute infantile spinal muscular atrophy (Werdnig– Hoffman disease) is one of the most common fatal autosomal reces- sive disorders of children. The disease frequency of approximately 1 in 25 000 in England results from a gene frequency of 1 in 160. Before the age of 6 months, babies become inactive, weak, and hypo- tonic, feed poorly, and are slow to attain motor milestones. They may be born with limb deformities and, in retrospect, fetal movements may have been sparse. The tongue is weak and may fasciculate. Head control is poor with proximally wasted areflexic limbs that tend to assume a frog-like position. Sadly, half of these infants die by 6 months, and almost all have succumbed by 18 months, usually to respiratory complications. Patients with types II, III, and IV spinal muscular atrophy have increasing levels of expression of SMN pro- tein, due to differences in copy number of an almost identical gene, SMN2. In type II (intermediate form), muscle weakness occurs be- fore 18 months; children can sit but not walk, and usually die in ado- lescence. Type III (chronic childhood form, Kugelberg–Welander disease) develops at any time after the age of 18 months to the early teens. Clinical features initially resemble Werdnig–Hoffmann dis- ease if the onset is early, but then follow a more benign course. More than 90% of patients can walk or sit unsupported at some time, al- though these abilities are often eventually lost. Tongue involvement occurs in approximately 50%, but significant dysphagia is unusual. Some patients develop respiratory insufficiency as a result of inter- costal muscle involvement. Proximal limb weakness and wasting are usually slowly progressive, but may sometimes stabilize spon- taneously. Those with severe early weakness may develop secondary spinal and joint deformities. The prognosis varies, but survival into middle age is usual. Type IV is the unusual adult-onset form of prox- imal spinal muscular atrophy, which starts between 15 to 60 years of age, usually in the fourth decade. The presentation is with slowly progressive proximal limb weakness and significant walking dis- ability does not usually occur until the sixth or seventh decade. Life expectancy is only slightly reduced. Distal muscles can also be in- volved and the tendon reflexes are usually lost. Bulbar involvement is uncommon. This type can be confused with progressive muscular atrophy; the lack of bulbar involvement, and indolent progression are helpful distinguishing features. In a few families from Brazil, adult-onset proximal spinal mus- cular atrophy was found to be inherited in an autosomal dominant manner, due to mutations in VAPB, and both typical and atypical ALS were also seen in the same families. Acute infantile proximal spinal muscular atrophy is pathologically distinct and unrelated to SMN protein. These disorders are associated with additional fea- tures, such as pontocerebellar hypoplasia, arthrogryposis, bone fractures, and lethal congenital contractures. Distal spinal muscular atrophies The distal spinal muscular atrophies (also called hereditary motor neuropathies or neuronopathies) are a phenotypically and genetic- ally diverse group of rare motor neuron diseases. Spinal muscular atrophy with respiratory distress presents with severe respiratory dis- tress, in infants without a mutation in SMN, and with a distal pattern of weakness. Other forms of the disease present either with upper limb predominant, lower limb predominant, or a scapuloperoneal distribution of weakness, resembling muscular dystrophy. Adult- onset variants exist. Distal spinal muscular atrophy with vocal cord paralysis has been described in two Welsh families. Genetic testing is complicated because of the large number of subtypes, some with as-yet unidentified mutations. X- linked recessive bulbospinal neuronopathy (Kennedy’s disease) This disorder almost always occurs in men, although rare cases of female manifesting carriers have been reported. Onset is usually in

the third to fifth decades of life. Kennedy's disease is caused by a mutation within the androgen receptor gene causing extra cytosine– adenine–guanine repeat sequences. Weakness usually first affects hand or pelvic girdle muscles and bulbar symptoms tend to develop later, sometimes up to 20 years after disease onset. Cramps are prom- inent and fasciculations are usually visible in the limb, tongue, and facial muscles. Characteristically, muscle contractions around the chin are induced by pursing the lips or grimacing. The disorder is slowly progressive and most patients survive into their seventh or eighth decade, except when bulbar involvement is unusually severe. The disorder is often misdiagnosed as MND until the unusually slow deterioration is questioned. Unlike MND, patients may have gynae- comastia, testicular atrophy, diabetes mellitus, and absent sensory nerve action potentials on electrophysiology. Hereditary bulbar palsy of infancy and childhood Brown–Vialetto–van Laere syndrome is a rare neurological disorder characterized by progressive pontobulbar palsy and bilateral sen- sorineural hearing loss, with variable age of onset. Deafness often precedes the development of VII, IX, X, XI, and XII cranial nerve palsies, which then develop relatively rapidly. With disease progres- sion, limb and respiratory weakness, UMN signs, cerebellar ataxia, and upper cranial nerve palsies develop. The same clinical presen- tation without deafness is known as Fazio–Londe disease; the two eponymous syndromes are now considered variants of a single dis- ease entity. A causative mutation was recently identified in C20orf54, a homologue of the rat riboflavin transporter protein, and promising early studies suggest that high-dose riboflavin may be beneficial. Hirayama disease This disorder is most commonly described in Asia, especially Japan and India, but can present in any population. It is usually sporadic and affects young men. The pathology has been hypothesized to in- volve microcirculatory changes induced by repeated or sustained neck flexion, but this is controversial and mechanisms remain in- completely understood. Hirayama disease presents with distal wasting and weakness of one hand or forearm, which progresses steadily for the first 2 years before either stabilizing or settling to a slow rate of subsequent progression. Characteristically, there is sparing of brachioradialis. The other arm can sometimes be affected later. Initially, there is often concern that the symptoms may rep- resent MND, but the expected UMN and bulbar involvement fails to materialize, and spread to the legs is unusual (although is de- scribed especially in Indian patients). Nerve conduction studies help

 exclude MND, focal entrapment neuropathies, or multifocal motor neuropathy with conduction block. MRI of the cervical spine will exclude syringomyelia or other spinal cord disease and should be performed on flexion and with contrast; a characteristic enhancing epidural crescent may be seen, which enlarges on flexion. Post-polio syndrome After two or more decades, very slowly progressive weakness may affect muscles previously involved by acute paralytic poliomyelitis. Although this predominantly affects the limbs, approximately 50% of the cases also have mild choking or dysphagia and weakness of the respiratory muscles, which may lead to hypercapnic respiratory failure. The sluggish deterioration, lack of UMN involvement, and previous history help distinguish post-polio syndrome from ALS. Electromyography reveals giant motor units typical of extensive reinnervation. The mechanisms are somewhat controversial; at least equally commonly, late deterioration after polio is due to secondary degenerative arthritis or fibromyalgia. Upper motor neuron syndromes The pure UMN syndromes are the rarest forms of motor neuron dis- ease. Imaging is mandatory to exclude structural or demyelinating disease of the spinal cord, foramen magnum, or brain. Deficiencies of vitamins B12 and copper need to be considered along with dopa- responsive dystonia and adrenomyeloneuropathy. Rarely, syphilis and HTLV-I (human T-lymphocytic virus type I) infections can cause a pure UMN syndrome. Management of spasticity is im- portant, but can be challenging. Primary lateral sclerosis The

primary lateral sclerosis variant of MND is a rare sporadic dis- ease (2% of cases) with an average age of onset of 50 years, and slow progression over an average of 15 years. The clinical features are all attributable to symmetrical degeneration of upper motor neurons destined for the spinal cord and bulbar region. A rare, even more slowly progressive hemiparetic variant also exists (Mills syndrome). Spasticity and weakness usually start insidiously in the legs and as- cend to involve the bulbar muscles later. Less commonly, patients present with pseudobulbar palsy. The associated emotional lability is often distressing for these patients but responds well to citalopram or amitriptyline. In the United States, dextromethorphan/quini- dine is used for emotional lability. Bladder function is generally well preserved, but dysfunction can occur late in the disease course. Electromyography does not reveal the muscle denervation expected in UMN-predominant forms of ALS, although some patients evolve to that condition. MRI may reveal atrophy of the precentral gyrus motor cortex, reflecting loss of the Betz cells from which the pyr- amidal tract originates. Central motor studies following electromag- netic stimulation of the motor cortex show delayed conduction. Hereditary spastic paraparesis Various forms of slowly progressive, symmetrical, spastic parapar- esis may be inherited, with onset often in the fourth to sixth dec- ades. The degree of leg spasticity often outweighs the severity of the weakness. Bulbar involvement is very rare, and arm function may be well preserved despite severe leg involvement. The condition is slowly progressive. It may remain asymptomatic in family members who are gene carriers. Urinary urgency and erectile dysfunction may occur. To date 56 loci have been identified, with pathogenic mutations identified in 41 genes. Clinically, the hereditary spastic parapareses are most conveniently divided into ‘pure’ and ‘compli- cated’ forms, the latter involving various additional features such as distal amyotrophy (termed Silver syndrome if early hand wasting), intellectual impairment, dementia, pigmentary retinopathy, optic atrophy, extrapyramidal features, sensory neuropathy, ataxia, or epilepsy. Inheritance is most commonly autosomal dominant, and these disorders are usually ‘pure’ and comprise abnormalities of various genes for proteins involved in intra-axonal trafficking, such as spastin, atlastin, or KIF5A, while other genetic mutations involve receptor accessory protein 1 (REEP-1), heat shock protein 60, and seipin. The less common autosomal recessive forms often produce ‘complicated’ phenotypes and mutations include those for paraplegin, spartin, and maspardin. X-linked mutations are rarer still and generally present in childhood with ‘complicated’ phenotypes. Lathyrism Neurolathyrism is a spastic paraparesis caused by regular con- sumption of the chickling pea (Lathyrus sativus) for some months. It is endemic in parts of India and outbreaks have occurred in China, Africa, and central Europe at times of famine. Patients, usually young men, present either subacutely or chronically with a spastic paraparesis and a characteristic scissoring gait in which the balls of the feet take most of the weight. Once it has developed, neurolathyrism is usually not progressive, but little or no recovery occurs even after chickling pea consumption ceases. A plant- derived excitotoxic amino acid, β-N-oxalyl-amino-L-alanine (BOAA), a glutamate analogue, is considered pathogenic. Konzo Konzo is a form of tropical myelopathy that can occur in epidemics at times of famine in sub-Saharan Africa. It appears to be due to dietary cyanogen consumption, resulting from insufficient soaking of the cassava roots used to produce flour. There is an abrupt onset of symmetrical spastic paraparesis, which is nonprogressive but per- manent. Blood cyanide levels are raised at the onset of disease. FURTHER READING Al Sultan A, et al. (2016). The genetics of amyotrophic lateral scler- osis: current insights. Degenerative Neurological and Neuromuscular Diseases, 6, 49–64. Bosch AM, et al. (2011). Brown–Vialetto–Van Laere and Fazio– Londe syndrome is associated with a riboflavin transporter defect mimicking mild MADD: a new inborn error of metabolism with po- tential treatment. J Inherit Metab Dis, 34, 159–64. Cooper-Knock J, et al. (2012). Clinico-pathological features in amyo- trophic

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