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neurodegeneration unrelated to a defect in iron metabolism. There are no specific treatments; iron binding may help slow progression, but this has not been established. FUNCTIONAL (PSYCHOGENIC) DISORDERS Virtually all movement disorders including tremor, tics, dystonia, myoclonus, chorea, ballism, and parkinsonism can be psychogenic in origin. The term functional neurologic symptom disorder (FND)/ conversion disorder has been suggested to replace the term psychogenic disorder in order to remove the criterion of psychological stress as a prerequisite for diagnosis; however, the terminology remains contro versial and both terms are used. A diagnosis can be made by identi fying neurologic signs that are specific to FNDs without reliance on psychological stressors or suggestive historical clues. Tremor affecting the upper limbs is the most common psychogenic movement disorder. Psychogenic movements can result from a somatoform or conversion disorder, malingering (e.g., seeking financial gain), or a factitious disorder (e.g., seeking psychological gain) (Chap. 463). Functional movement disorders are relatively common (estimated at 2–3% of patients seen in a movement disorder clinic), more frequent in women, disabling for the patient and family, and expensive for society. Clinical features suggesting a functional or psychogenic movement disorder include an acute onset with a pattern of abnormal movement that is inconsistent with the phenotype of a known movement disorder. Diag nosis is based on the nonorganic quality of the movement, the absence of findings of an organic disease process, and positive features that spe cifically point to a functional illness such as variability and distractibil ity. For example, in a functional tremor disorder, the magnitude of the tremor is increased with attention and diminishes or even disappears when the patient is distracted by being asked to perform a different task or is unaware that he or she is being observed. This is the opposite of what is seen with an organic tremor where the magnitude of tremor is increased with distraction and tends to be reduced when observed. Other positive features suggesting a psychogenic problem include vari able tremor frequency, entrainment of the tremor frequency with the frequency of a designated movement in the contralateral limb such as tapping, and a response to placebo interventions. Associated features can include nonanatomic sensory findings, give-way weakness, astasiaabasia (an odd, gyrating gait or posture) (Chap. 28), and multiple somatic complaints with no underlying pathology

(somatoform disor der). Comorbid psychiatric problems such as anxiety, depression, and emotional trauma may be present but are not necessary for the diagno sis, which is why some prefer to call the movement disorder functional rather than psychogenic. Functional movement disorders typically occur as an isolated entity but may be seen in association with an underlying organic problem. The diagnosis can usually be made based on history and clinical features alone, and unnecessary tests or medi cations can be avoided. If there are underlying psychiatric problems, they should be identified and treated, but as noted, many patients with functional movement disorders have no obvious psychiatric pathology. Treatment of FND starts with explaining the diagnosis to the patient in a nonthreatening manner, but many are resistant to accepting this diag nosis. Psychological therapies (especially cognitive-behavioral) are the method of choice. An increasing role of physiotherapy has also recently been recognized, and a recent trial of physiotherapy and cognitivebehavioral therapy in combination was found to effectively improve symptoms in nearly half of patients. Comorbid depression, anxiety, and pain may be treated pharmacologically. Patients with hypochondriasis, factitious disorders, and malingering have a poor prognosis. ■ ■FURTHER READING Baumgartner AJ et al: Novel targets in deep brain stimulation for movement disorders. Neurosurg Rev 45:2593, 2022. Bhatia KP et al: Tremor Task Force of the International Parkinson and Movement Disorder Society. Mov Disord 33:75, 2018. Billnitzer A, Jankovic J: Current management of tics and Tourette syndrome: Behavioral, pharmacologic, and surgical treatments. Neu rotherapeutics 17:1681, 2020. Elias WJ, Shah BB: Essential tremor. JAMA 332:418, 2024.

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Amyotrophic Lateral

Sclerosis and Other Motor Neuron Diseases Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases AMYOTROPHIC LATERAL SCLEROSIS Amyotrophic later sclerosis (ALS) is the most common progressive motor neuron disease. It is a prime example of a neurodegenerative disease and is arguably the most devastating of the neurodegenera tive disorders. ■ ■PATHOLOGY The pathologic hallmark of motor neuron degenerative disorders is death of lower motor neurons (consisting of anterior horn cells in the spinal cord and their brainstem homologues innervating bulbar muscles) and upper, or corticospinal, motor neurons (originating in layer five of the motor cortex and descending via the pyramidal tract to synapse with lower motor neurons, either directly or indirectly via interneurons) (Chap. 26). Although at its onset ALS may involve selec tive loss of function of only upper or lower motor neurons, it ultimately causes progressive loss of both categories of motor neurons. Indeed, in the absence of clear involvement of both motor neuron

types, the diagnosis of ALS is questionable. In a subset of cases, ALS arises concurrently with frontotemporal dementia (Chap. 443); in these instances, there is degeneration of frontotemporal cortical neurons and corresponding cortical atrophy. Other motor neuron diseases involve only particular subsets of motor neurons (Tables 448-1 and 448-2). Thus, in bulbar palsy and spinal muscular atrophy (SMA, predominantly in children) and pro gressive muscular atrophy (PMA, in adults), the lower motor neurons of brainstem and spinal cord, respectively, are most severely involved. By contrast, pseudobulbar palsy, primary lateral sclerosis (PLS), and hereditary spastic paraplegia (HSP) affect only upper motor neurons innervating the brainstem and spinal cord. In each of these diseases, the affected motor neurons undergo shrinkage, often with accumulation of the pigmented lipid (lipofuscin) that normally develops in these cells with advancing age. In ALS, the motor neuron cytoskeleton is typically affected early in the illness. Focal enlargements are frequent in proximal motor axons; ultrastruc turally, these “spheroids” are composed of accumulations of neuro filaments and other proteins. Commonly in both sporadic and familial ALS, the affected neurons demonstrate ubiquitin-positive aggregates, often associated with the protein TDP43 (see below). Also seen is

TABLE 448-1 Etiology of Motor Neuron Disorders DIAGNOSTIC CATEGORY INVESTIGATION Structural lesions Parasagittal or foramen magnum MRI scan of head (including foramen magnum and cervical spine) tumors Cervical spondylosis Chiari malformation of syrinx Spinal cord arteriovenous malformation Infections Bacterial—tetanus, Lyme Viral—poliomyelitis, herpes zoster Retroviral—myelopathy CSF exam, culture Lyme titer Antiviral antibody HTLV-1 titers Intoxications, physical agents Toxins—lead, aluminum, others Drugs—strychnine, phenytoin Electric short, x-irradiation 24-h urine for heavy metals Serum lead level PART 13 Neurologic Disorders Immunologic mechanisms Plasma cell dyscrasias Autoimmune polyradiculopathy Motor neuropathy with conduction Complete blood counta Sedimentation ratea Total proteina Anti-GM1 antibodiesa block Paraneoplastic Paracarcinomatous Anti-Hu antibody MRI scan, bone marrow biopsy Metabolic Hypoglycemia Hyperparathyroidism Hyperthyroidism Deficiency of folate, vitamin B12, Fasting blood sugara Routine chemistries including calciuma PTH Thyroid functiona Vitamin B12, vitamin E, folatea vitamin E Malabsorption Deficiency of copper, zinc Mitochondrial dysfunction Serum zinc, coppera 24-h stool fat, carotene, prothrombin time Fasting lactate, pyruvate, ammonia Consider mtDNA Hyperlipidemia Lipid electrophoresis Hyperglycinuria Urine and serum amino acids CSF amino acids Hereditary disorders C9orf72 Superoxide dismutase TDP43 FUS/TLS Androgen receptor defect WBC DNA for mutational analysis (Kennedy’s disease) aShould be obtained in all cases. Abbreviations: CSF, cerebrospinal fluid; FUS/TLS, fused in sarcoma/translocated in liposarcoma; HTLV-1, human T-cell lymphotropic virus; MRI, magnetic resonance imaging; PTH, parathyroid; WBC, white blood cell. proliferation of astroglia and microglia, the inevitable accompaniment of all degenerative processes in the central nervous system (CNS). The death of the peripheral motor neurons in the brainstem and spinal cord leads to denervation and atrophy of the corresponding muscle fibers. Histochemical and electrophysiologic evidence indicates that in the early phases of the illness denervated muscle can be rein nervated by sprouting of nearby distal motor nerve terminals, although reinnervation in this disease is considerably less extensive than in most other disorders affecting motor neurons (e.g., poliomyelitis, peripheral neuropathy). As denervation progresses, muscle atrophy is readily recognized in muscle biopsies and on clinical examination. This is the basis for the term amyotrophy. The loss of cortical motor neurons results in thinning of the corticospinal tracts that travel via the inter nal capsule (Fig. 448-1) and pyramidal tracts in the brainstem to the lateral and anterior white matter columns of the spinal cord. The loss of fibers in

the lateral columns and resulting fibrillary gliosis impart a particular firmness (lateral sclerosis). A remarkable feature of the

TABLE 448-2 Sporadic Motor Neuron Diseases CHRONIC ENTITY Upper and lower motor neuron Amyotrophic lateral sclerosis Predominantly upper motor neuron Primary lateral sclerosis Predominantly lower motor neuron Multifocal motor neuropathy with conduction block Motor neuropathy with paraproteinemia or cancer Motor predominant peripheral neuropathies Other Associated with other neurodegenerative disorders Secondary motor neuron disorders (see Table 448-1) Acute Poliomyelitis Herpes zoster Coxsackie virus West Nile virus disease is the selectivity of neuronal cell death. By light microscopy, the entire sensory apparatus and cerebellar structures that control the coordination of movement remain intact. Except in cases of fronto temporal dementia, the components of the brain required for cognitive processing are also preserved. However, immunostaining indicates that neurons bearing ubiquitin, a marker for degeneration, are also detected in nonmotor systems. Moreover, studies of glucose metabolism in the illness also indicate that there is neuronal dysfunction outside of the motor system. Pathologic studies reveal proliferation of microglial cells and astrocytes in affected regions; in some cases, this phenomenon, designated neuroinflammation, can be visualized using positron emis sion tomography (PET) scanning for ligands that are recognized by activated microglia. Within the motor system, there is some selectivity FIGURE 448-1 Amyotrophic lateral sclerosis. Axial T2-weighted magnetic resonance imaging (MRI) scan through the lateral ventricles of the brain reveals abnormal high signal intensity within the corticospinal tracts (arrows). This MRI feature represents an increase in water content in myelin tracts undergoing Wallerian degeneration secondary to cortical motor neuronal loss. This finding is commonly present in ALS but can also be seen in AIDS-related encephalopathy, infarction, or other disease processes that produce corticospinal neuronal loss in a symmetric fashion.

of involvement. Thus, motor neurons required for ocular motility remain unaffected, as do the parasympathetic neurons in the sacral spinal cord (the nucleus of Onufrowicz, or Onuf) that innervate the sphincters of the bowel and bladder. ■ ■CLINICAL MANIFESTATIONS The manifestations of ALS are somewhat variable depending on whether corticospinal neurons or lower motor neurons in the brain stem and spinal cord are more prominently involved. With lower motor neuron dysfunction and early denervation, typically the first evidence of the disease is insidiously developing asymmetric weakness, usually first evident distally in one of the limbs. A detailed history often discloses recent development of cramping with volitional movements, typically in the early hours of the morning (e.g., while stretching in bed). Weakness caused by denervation is associated with progressive wasting and atrophy of muscles and, particularly early in the illness, spontaneous twitching of motor units, or fasciculations. In the hands, a preponderance of extensor over flexor weakness is common. When the initial denervation involves bulbar rather than limb muscles, the problem at onset is difficulty with chewing, swallowing, and move ments of the face and tongue. Rarely, early involvement of the muscles of respiration may lead to death before the disease is far advanced elsewhere. With prominent corticospinal involvement, there is hyper activity of the muscle-stretch reflexes (tendon jerks) and, often, spastic resistance to passive movements of the affected limbs. Patients with significant reflex hyperactivity complain of muscle stiffness often out of proportion to weakness. Degeneration of the corticobulbar projections innervating the brainstem results in dysarthria and exaggeration of the motor expressions of emotion. The latter leads to involuntary excess in weeping or laughing (pseudobulbar affect).

Virtually any muscle group may be the first to show signs of dis ease, but, as time passes, more and more muscles become involved until ultimately the disorder takes on a symmetric distribution in all regions. It is characteristic of ALS that, regardless of whether the initial disease involves upper or lower motor neurons, both will eventually be implicated. Even in the late stages of the illness, sensory, bowel and bladder, and cognitive functions are preserved. Even when there is severe brainstem disease, ocular motility is spared until the very late stages of the illness. As noted, in some cases (particularly those that are familial), ALS develops concurrently with frontotemporal dementia, characterized by early behavioral abnormalities with prominent behav ioral features indicative of frontal lobe dysfunction. A committee of the World Federation of Neurology has established diagnostic guidelines for ALS. Essential for the diagnosis is simulta neous upper and lower motor neuron involvement with progressive weakness and the exclusion of all alternative diagnoses. The disorder is ranked as “definite” ALS when three or four of the following are involved: bulbar, cervical, thoracic, and lumbosacral motor neurons. When two sites are involved, the diagnosis is “probable,” and when only one site is implicated, the diagnosis is “possible.” An exception is made for those who have progressive upper and lower motor neuron signs at only one site and a mutation in the gene encoding superoxide dismutase (SOD1; see below). It is now recognized that another clinical manifestation in most cases of ALS is the presence in cerebrospinal fluid (CSF) and serum of markers of neurodegeneration, such as elevated levels of neurofilament light chains (Nfl) or phosphorylated neurofilament heavy chains; some markers of inflammation (e.g., monocyte chemoattractant protein 1) are also elevated. Higher levels of serum or CSF Nfl are correlated with more aggressive disease and more rapid disease progression. Accord ingly, these CSF biomarkers are increasingly used as endpoints in clinical trials.
■ ■EPIDEMIOLOGY The illness is relentlessly progressive, leading to death from respiratory paralysis; the median survival is from 3 to 5 years. There are very rare reports of stabilization or even regression of ALS. In most societies, there is an incidence of 1–3 per 100,000 and a prevalence of 3–5 per 100,000. It is striking that about 1 in 500 deaths in North America

and Western Europe (and probably elsewhere) are due to ALS; this finding predicts that >500,000 individuals now alive in the United States will die of ALS. Several endemic foci of higher prevalence exist in the western Pacific (e.g., in specific regions of Guam or Papua New Guinea). In the United States and Europe, men are somewhat more fre quently affected than women. Epidemiologic studies have incriminated risk factors for this disease including exposure to pesticides and insec ticides, silica, smoking, and possibly service in the military. Although ALS is overwhelmingly a sporadic disorder, some 10% of cases are inherited as an autosomal dominant trait.

■ ■FAMILIAL ALS Several forms of selective motor neuron disease are inheritable (Table 448-3). Familial ALS (FALS) involves both corticospinal and lower motor neurons. Apart from its inheritance as an autosomal dominant trait, it is clinically indistinguishable from sporadic ALS. Genetic studies have identified mutations in multiple genes, includ ing those encoding the protein C9orf72 (open reading frame 72 on chromosome 9), cytosolic enzyme SOD1 (superoxide dismutase), the RNA binding proteins TDP43 (encoded by the TAR DNA bind ing protein gene), and fused in sarcoma/translocated in liposarcoma (FUS/TLS), as the most common causes of FALS. Mutations in C9orf72 account for ~45–50% of FALS and perhaps 5–10% of sporadic ALS cases. Mutations in SOD1 explain another 20% of cases of FALS, whereas TDP43 and FUS/TLS each represent about 5% of familial cases. Mutations in several other genes (e.g., NEK1, optineurin, TBK1, KIF5A, TUBA4, and PFN11) each cause ~1% of cases. CHAPTER 448 Amyotrophic Lateral Sclerosis and Other Motor

Neuron Diseases Rare mutations in other genes are also clearly implicated in ALS-like diseases. Thus, a familial, dominantly inherited motor disorder that in some individuals closely mimics the ALS phenotype arises from mutations in a gene that encodes a vesicle-binding protein. Mutations in senataxin, a helicase, cause an early-adult-onset, slowly evolving ALS variant. Kennedy's syndrome is an X-linked, adult-onset disorder that may mimic ALS, as described below. Tau gene mutations usually underlie frontotemporal dementia but in some instances may be asso ciated with prominent motor neuron findings. Genetic analyses are also beginning to illuminate the pathogenesis of some childhood-onset motor neuron diseases. For example, a slowly disabling degenerative, predominantly upper motor neuron disease that starts in the first decade is caused by mutations in a gene that expresses a novel signaling molecule with properties of a guanineexchange factor, termed alsin. ■ ■DIFFERENTIAL DIAGNOSIS Because ALS is currently untreatable, it is imperative that poten tially remediable causes of motor neuron dysfunction be excluded (Table 448-1). This is particularly true in cases that are atypical by virtue of (1) restriction to either upper or lower motor neurons, (2) involvement of neurons other than motor neurons, and (3) evidence of motor neuronal conduction block on electrophysiologic testing. Com pression of the cervical spinal cord or cervicomedullary junction from tumors in the cervical regions or at the foramen magnum or from cer vical spondylosis with osteophytes projecting into the vertebral canal can produce weakness, wasting, and fasciculations in the upper limbs and spasticity in the legs, closely resembling ALS. The absence of cranial nerve involvement may be helpful in differentiation, although some foramen magnum lesions may compress the twelfth cranial (hypoglossal) nerve, with resulting paralysis of the tongue. Absence of pain or of sensory changes, normal bowel and bladder function, normal radiologic studies of the spine, and normal CSF all favor ALS. Where doubt exists, magnetic resonance imaging (MRI) scans and possibly contrast myelography should be performed to visualize the cervical spinal cord. Another important entity in the differential diagnosis of ALS is multifocal motor neuropathy with conduction block (MMCB), discussed below. A diffuse, lower motor axonal neuropathy mimicking ALS sometimes evolves in association with hematopoietic disorders such as lymphoma or multiple myeloma. In this clinical setting, the presence of an M-component in serum should prompt consideration of a bone

TABLE 448-3 Genetic Motor Neuron Diseases GENE SYMBOL GENE NAME INHERITANCE DISEASE I. Selected Upper and Lower Motor Neurons (Familial ALS) + Frontotemporal Dementia (FTD) ALS/ALS-FTD C9ORF72 Chromosome 9 open reading frame 72 AD 45% (6–10% SALS) Adult Regulates vesicle trafficking ALS SOD1 Cu/Zn superoxide dismutase 1 AD 20% (2% SALS) Adult Protein antioxidant ALS/ALS-FTD TARDBP TAR DNA binding protein AD 5% Adult DNA, RNA binding ALS/ALS-FTD FUS/TLS Fused in sarcoma/ translocated in liposarcoma AD 5% Adult DNA, RNA binding ALS/ALS-FTD CCNF E3 ubiquitin ligase cyclin F AD 2% Adult Mediates ubiquitination ALS NEK1 NMA-related kinase AR 2% Adult Microtubules, nuclear transport PART 13 Neurologic Disorders ALS/ALS-FTD TBK1 Tank binding kinase 1 AD 2% Adult Regulates autophagy, inflammation ALS KIF5A Kinesin family member 5A AD 1–2% Early adult Microtubule motor CMT ALS PFN1 Profilin 1 AD ~1% Adult Involved in actin polymerization ALS/ALS-FTD OPTN Optineurin AD/AR ~1% Adult Attenuates NF-κB ALS SPG11 Spastic paraplegia 11 AR ~1% Adult Vesicle trafficking Spastic paraplegia ALS SETX Senataxin AD ~1% Late juvenile DNA helicase Late childhood onset ALS/ALS-FTD VCP Valosin-containing protein AD ~ 1% Adult ATPase Paget's, myopathy ALS-FTD UBQLN2 Ubiquilin 2 XR <1% Adult or juvenile ALS-FTD CHMP2B Chromatin modifying protein 2B AD <1% Adult Chromatin binding protein ALS-FTD MAPT Microtubule Associated Protein Tau AD <1% Adult Cytoskeletal protein Usually causes only FTD ALS2 ALS2 Alsin

AR <1% Juvenile GEF signaling Corticobulbar/ corticospinal may mimic PLS ALS-FTD CHMP2B Chromatin modifying protein 2B AD <1% Adult Chromatin binding protein II. Lower Motor Neurons Spinal muscular atrophies SMN Survival motor neuron AR 1/10,000 live births Infancy RNA metabolism GM2-gangliosidosis 1. Sandhoff's disease HEXB Hexosaminidase B AR Childhood Ganglioside recycling 2. AB variant GM2A GM2-activator protein AR Childhood Ganglioside recycling 3. Adult Tay-Sachs HEXA Hexosaminidase A AR Childhood Ganglioside recycling disease X-linked spinobulbar muscular atrophy AR Androgen receptor XR Adult Nuclear signaling III. Upper Motor Neuron (Selected HSPs) SPG3A ATL1 Atlastin AD 10% AD FSP Childhood GTPase—vesicle recycling SPG4 SPAST Spastin AD 50–60% AD FSP Early adulthood ATPase family—SPG10 KIF5A Kinesin heavy chain isoform 5A AD 10% AD FSP Second–third decade SPG31 REEP1 Receptor Expression Enhancing Protein 1 AD 10% AD FSP Early Mitochondrial protein Rarely, amyotrophy SPG5 CYP7B1 Cytochrome P450 AR 5–10% AR FSP Variable Degrades endogenous substances SPG7 SPG7 Paraplegin AR 5–10% AR FSP Variable Mitochondrial protein Rarely, optic atrophy, ataxia, rarely PLS

U.S. FREQUENCY

% FALS USUAL ONSET PROTEIN FUNCTION UNUSUAL FEATURES May also be associated with parkinsonism, PLS Protein degradation Some sensory loss microtubule associate Motor-associated protein ± Peripheral neuropathy, retardation Sensory loss (Continued)

TABLE 448-3 Genetic Motor Neuron Diseases (Continued) GENE SYMBOL GENE NAME INHERITANCE DISEASE SPG11 SPG11 Spatacsin AR 20–70% AR FSP depends on ethnicity SPG2 PLP Proteolipid protein XR <1% Early childhood Myelin protein Sometimes multiple CNS features Adrenoleukodystrophy ALDP Adrenoleukodystrophy protein XR <1% Early adulthood ATP binding Abbreviations: AD, autosomal dominant; ALS, amyotrophic lateral sclerosis; AR, autosomal recessive; CNS, central nervous system; CMT, Charcot-Marie-Tooth; BSCL2, Bernadelli-Seip congenital lipodystrophy 2B; FALS, familial amyotrophic lateral sclerosis; FSP, familial spastic paraplegia; FUS/TLS, fused in sarcoma/translocated in liposarcoma; GEF, guanidine nucleotide exchange factor; HSP, hereditary spastic paraplegia; NF-κB, nuclear factor-κB; PLS, primary lateral sclerosis; SALS, sporadic amyotrophic lateral sclerosis; TDP43, Tar DNA binding protein 43 kd; XR, X-linked recessive. marrow biopsy. Lyme disease (Chap. 191) may also cause an axonal, lower motor neuropathy, although typically with intense proximal limb pain and a CSF pleocytosis. Other treatable disorders that occasionally mimic ALS are chronic lead poisoning and thyrotoxicosis. These disorders may be suggested by the patient's social or occupational history or by unusual clini cal features. When the family history is positive, disorders involving the genes encoding C9orf72, cytosolic SOD1, TDP43, FUS/TLS, and adult hexosaminidase A or α-glucosidase deficiency (Chap. 429) must be excluded. These are readily identified by appropriate laboratory tests; importantly, panels for simultaneous analysis of multiple ALS and frontotemporal dementia (FTD) genes are now commercially available. Benign fasciculations are occasionally a source of concern because on inspection they resemble the fascicular twitchings that accompany motor neuron degeneration. The absence of weakness, atrophy, or denervation phenomena on electrophysiologic examina tion usually excludes ALS or other serious neurologic disease. Patients who have recovered from poliomyelitis may experience a delayed deterioration of motor neurons that presents clinically with progres sive weakness, atrophy, and fasciculations. Its cause is unknown, but it is thought to reflect sublethal prior injury to motor neurons by poliovirus (Chap. 210). Rarely,

ALS develops concurrently with features indicative of more widespread neurodegeneration. Neuropsychological testing may detect subtle cognitive impairment in ~15% of cases that clinically are purely ALS; these cognitive deficits worsen with disease progression. Impor tantly, one often encounters the combination of ALS and FTD in indi viduals who harbor C9orf72 mutations. The simultaneous occurrence of these disorders reflects shared embryologic origins and transcription factor expression in corticospinal motor neurons and neurons impli cated in FTD (von Economo neurons). Overall, up to 40% of FTD cases harbor mutations in the C9orf72 gene. Beyond C9orf72, several other ALS genes can trigger both ALS and FTD (see Table 448-3). As another example of an atypical phenotype, prominent amyotrophy has been described as a dominantly inherited disorder in individuals with bizarre behavior and a movement disorder suggestive of parkinsonism; many such cases have now been ascribed to mutations that alter the expression of tau protein in the brain (Chap. 443). An ALS-like disor der has also been described in some individuals with chronic traumatic encephalopathy (Chap. 454), associated with deposition of TDP43 and neurofibrillary tangles in motor neurons. ■ ■PATHOGENESIS The cause of sporadic ALS is not well defined, in part because there is no animal model for this form of ALS. Strikingly, motor neurons derived from stem cells of individuals with sporadic ALS can display diminished viability, suggesting that heritable factors play a role. Several mechanisms that impair motor neuron viability have been elucidated in rodents that harbor transgenes with mutant SOD1, pro filin-1, or C9orf72. One may loosely group the genetic causes of ALS into three categories. In one group, the primary problem is inherent

U.S. FREQUENCY

% FALS USUAL ONSET PROTEIN FUNCTION UNUSUAL FEATURES Predominantly childhood Cytosolic,? membrane-associated Some sensory loss, thin corpus callosum; may mimic ALS (ALS5) Possible adrenal insufficiency, CNS inflammation transporter protein CHAPTER 448 instability of the mutant proteins, with subsequent perturbations in protein degradation (SOD1, ubiquilin-1 and 2, p62). In the second category, the causative mutant genes perturb RNA processing, trans port, and metabolism (C9orf73, TDP43, FUS). In the case of C9orf72, the molecular pathology is an expansion of an intronic hexanucleo tide repeat (-GGGGCC-) beyond an upper normal of 30 repeats to hundreds or even thousands of repeats. As observed in other intronic repeat disorders such as myotonic dystrophy (Chap. 460) and spi nocerebellar atrophy type 8 (Chap. 450), the expanded intronic repeats generate expanded RNA repeats that form intranuclear foci and may confer toxicity by sequestering transcription factors or by undergoing noncanonical protein translation across all possible reading frames of the expanded RNA tracts. Importantly, the latter process generates lengthy dipeptides that are detected in the spinal fluid and are a unique biomarker for C9orf72 ALS. TDP43 and FUS are multifunctional proteins that bind RNA and DNA and shuttle between the nucleus and the cytoplasm, playing multiple roles in the control of cell proliferation, DNA repair and transcription, and gene translation, both in the cytoplasm and locally in dendritic spines in response to electrical activity. How mutations in FUS/TLS provoke motor neuron cell death is not clear, although this may represent loss of function of FUS/TLS in the nucleus or an acquired, toxic function of the mutant proteins in the cytosol. In the third group of ALS genes, the primary problem is defective axonal cytoskeleton and transport (dynactin, profilin-1). It is striking that variants in other genes influ ence survival in ALS but not ALS susceptibility. Intermediate-length polyglutamine-coding expansions (-CAG-) in the gene ataxin-2 confer increased ALS susceptibility; suppression of ataxin-2 expres sion extends survival in transgenic ALS mice. Beyond the upstream, primary defects, it is also evident that the ultimate neuronal cell death process is complex,

involving multiple cellular processes acting in diverse components of the motor neuron (dendrites, cell body, axons, neuromuscular junction) to accelerate cell death. These include but are not limited to excitotoxicity, defective autophagy, impairment of axonal transport, oxidative stress, activation of endoplasmic reticu lum stress and the unfolded protein response, and mitochondrial dysfunction. In addition, the hexanucleotide expansions that cause C9orf72 ALS disrupt nucleocytoplasmic transport; the importance of this observation is underscored by the finding that mutations in the gene encoding GLE1, a protein that mediates mRNA export, cause an aggressive, infantile motor neuron disease. Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases Multiple studies have convincingly demonstrated that proliferating, activated nonneuronal cells such as microglia and astrocytes impor tantly influence the disease course, at least in ALS-transgenic mice. A striking additional finding in ALS and most neurodegenerative dis orders is that miscreant proteins arising from gene defects in familial forms of these diseases are often implicated in sporadic forms of the same disorder. For example, some reports propose that nonheritable, posttranslational modifications in SOD1 are pathogenic in sporadic ALS; indeed, SOD1 aggregates are sometimes observed in spinal cord in sporadic ALS without SOD1 mutations.

TREATMENT Amyotrophic Lateral Sclerosis No treatment arrests the underlying pathologic process in ALS. The drug riluzole (100 mg/d) was approved for ALS because it produces a modest lengthening of survival. In one trial, the survival rate at 18 months with riluzole was similar to placebo at 15 months. The mechanism of this effect is not known with certainty; riluzole may reduce excitotoxicity by diminishing glutamate release. Riluzole is generally well tolerated; nausea, dizziness, weight loss, and elevated liver enzymes occur occasionally. A second drug, edaravone, has also been approved by the U.S. Food and Drug Administration (FDA) based on a single 6-month study in a highly selected ALS population that demonstrated a modest reduction in the trajectory of worsening on an ALS disability scale; survival was not included as an endpoint. This drug, which is believed to act as an antioxidant, was initially administered via recurring monthly 10-day series of daily intravenous infusions. A formulation for oral use is now available. PART 13 Neurologic Disorders Interventions such as antisense oligonucleotides (ASO) and microRNAs that diminish expression of mutant SOD1 protein prolong survival in transgenic-ALS rodent models and are also now under investigation in SOD1-mediated ALS. Tofersen, an ASO that suppresses SOD1 expression following intrathecal delivery, is now FDA approved for SOD1-mediated ALS. Pilot studies of an ASO targeting FUS/TLS have also been promising. Pathophysi ologic studies of cell lines and animal models incorporating mutant SOD1, C9orf72, and other ALS genes have disclosed diverse targets for therapy; consequently, multiple therapies are presently in clini cal trials for ALS including experimental trials of small molecules, mesenchymal stem cells, and immunosuppression. In the absence of a primary therapy for ALS, a variety of reha bilitative aids may substantially assist ALS patients. Foot-drop splints facilitate ambulation by obviating the need for excessive hip flexion and by preventing tripping on a floppy foot. Fingerextension splints can potentiate grip. Respiratory support may be life-sustaining. For patients electing against long-term ventilation by tracheostomy, positive-pressure ventilation by mouth or nose provides transient (weeks to months) relief from hypercarbia and hypoxia. Also extremely beneficial for some patients is a respiratory device (cough assist machine) that produces an artificial cough. This is highly effective in clearing airways and preventing aspira tion pneumonia. When bulbar disease prevents normal chewing and swallowing, gastrostomy is uniformly helpful, restoring nor mal nutrition and hydration. Fortunately, an increasing variety of speech synthesizers are now available to augment speech when there is advanced bulbar palsy. These facilitate oral communication and may be

effective for telephone use. In contrast to ALS, several of the disorders (Tables 448-1 and 448-3) that bear some clinical resemblance to ALS are treatable. For this reason, a careful search for causes of secondary motor neuron disease is warranted. OTHER MOTOR NEURON DISEASES ■ ■SELECTED LOWER MOTOR NEURON DISORDERS In these motor neuron diseases, the peripheral motor neurons are affected without evidence of involvement of the corticospinal motor system (Tables 448-1, 448-2, and 448-3). X-Linked Spinobulbar Muscular Atrophy (Kennedy's

Disease) This is an X-linked lower motor neuron disorder in which progressive weakness and wasting of limb and bulbar muscles begins in males in mid-adult life and is conjoined with androgen insensitivity mani fested by gynecomastia and reduced fertility (Chap. 403). In addition to gynecomastia, which may be subtle, two findings distinguishing this disorder from ALS are the absence of signs of pyramidal tract disease (spasticity) and the presence of a subtle sensory neuropathy in some

patients. The underlying molecular defect is an expanded trinucleotide repeat (CAG) in the first exon of the androgen receptor gene on the X chromosome. An inverse correlation appears to exist between the number of CAG repeats and the age of onset of the disease. Adult Tay-Sachs Disease Several reports have described adultonset, predominantly lower motor neuropathies arising from defi ciency of the enzyme β-hexosaminidase (hex A). These tend to be distinguishable from ALS because they are very slowly progressive and in some cases may have been symptomatic for years; dysarthria and radiographically evident cerebellar atrophy may be prominent. In rare cases, spasticity may also be present, although it is generally absent (Chap. 429). Spinal Muscular Atrophy The SMAs are a family of selective lower motor neuron diseases of early onset. Despite some pheno typic variability (largely in age of onset), the defect in the majority of families with SMA is loss of a protein (SMN, for survival motor neuron) that is important in the formation and trafficking of RNA complexes across the nuclear membrane. Neuropathologically, these disorders are characterized by extensive loss of large motor neurons; muscle biopsy reveals evidence of denervation atrophy. Several clini cal forms exist. Infantile SMA (SMA I, Werdnig-Hoffmann disease) has the earliest onset and most rapidly fatal course. In some instances, it is apparent even before birth, as indicated by decreased fetal move ments late in the third trimester. Though alert, afflicted infants are weak and floppy (hypotonic) and lack muscle-stretch reflexes. Death generally ensues within the first year of life. Chronic childhood SMA (SMA II) begins later in childhood and evolves with a more slowly progressive course. Juvenile SMA (SMA III, Kugelberg-Welander disease) manifests during late childhood and runs a slow, indolent course. Unlike most denervating diseases, in this chronic disorder, weakness is greatest in the proximal muscles; indeed, the pattern of clinical weakness can suggest a primary myopathy such as limbgirdle dystrophy. Electrophysiologic and muscle biopsy evidence of denervation distinguish SMA III from the myopathic syndromes. Remarkably, two treatments have shown dramatic benefit in infan tile SMA. One, nusinersen, now an approved therapy, entails admin istering small oligonucleotides that alter mRNA splicing of one of the SMN genes, generating sufficient normal SMN protein to pro vide clinical benefit (including prolonged survival). The other treat ment uses systemically administered adeno-associated virus (AAV) to deliver the missing SMN gene to motor neurons and other cells. Multifocal Motor Neuropathy with Conduction Block In this disorder, lower motor neuron function is regionally and chroni cally disrupted by focal blocks in conduction. Many cases have ele vated serum titers of mono- and polyclonal antibodies to ganglioside GM1; it is hypothesized that the antibodies produce selective, focal, paranodal demyelination of motor neurons. MMCB is not typically associated with corticospinal signs. In contrast with ALS, MMCB may respond dramatically

to therapy such as IV immunoglobulin or chemotherapy; thus, it is imperative that MMCB be excluded when considering a diagnosis of ALS. Other Forms of Lower Motor Neuron Disease In individual families, other syndromes characterized by selective lower motor neuron dysfunction in an SMA-like pattern have been described. There are rare X-linked and autosomal dominant forms of apparent SMA. There is an ALS variant of juvenile onset, the Fazio-Londe syndrome, that involves mainly the musculature innervated by the brainstem. A component of lower motor neuron dysfunction is also found in degenerative disorders such as Machado-Joseph disease and the related olivopontocerebellar degenerations (Chap. 450). Finally, a group of lower motor neuron disorders, sometimes mim icking Charcot-Marie-Tooth disease, and sometimes spinal muscular atrophy, are caused by mutations in the enzymes (tRNA synthetases) that charge tRNA with specific amino acids, an early step in protein synthesis.

Revision #1
Created 2026-01-06 16:35:48 UTC by Omar Ayman
Updated 2026-01-06 16:35:48 UTC by Omar Ayman