signs at only one site and a mutation in the gene encoding superoxide dismutase (SOD1; see below).

EPIDEMIOLOGY

The illness is relentlessly progressive, leading to death from respiratory paralysis; the median survival is from 3–5 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 1000 adult deaths in North America and Western Europe (and probably elsewhere) are due to ALS; this finding predicts that some 300,000 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, males are somewhat more frequently affected than females. Epidemiologic studies have incriminated risk factors for this disease including exposure to pesticides and insecticides, smoking, and, in one report, service in the military. Although ALS is overwhelmingly a sporadic disorder, some 5–10% of cases are inherited as an autosomal dominant trait.

FAMILIAL ALS

Several forms of selective motor neuron disease are inheritable (Table 452-3). 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, including 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 binding protein gene), and FUS/TLS (fused in sarcoma/translocated in liposarcoma), as the most common causes of FALS. Mutations in C9orf72 account for ~45–50% of FALS and perhaps 4–5% 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. It has recently been reported that ~1–2% of cases are caused by mutations in genes encoding the proteins optineuron and profilin-1 as well.

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. A predominantly lower motor neuron disease with early hoarseness due to laryngeal dysfunction has been ascribed to mutations in the gene encoding the cellular accessory motor protein dynactin. 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.

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 guanine-exchange factor, termed *alsin*.

DIFFERENTIAL DIAGNOSIS

Because ALS is currently untreatable, it is imperative that potentially remediable causes of motor neuron dysfunction be excluded (Table 452-1). 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. Compression of the cervical spinal cord or cervicomedullary junction from tumors in the cervical regions or at the foramen magnum or from cervical 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 roentgenographic studies of the spine, and normal cerebrospinal fluid (CSF) all favor ALS. Where doubt exists, magnetic resonance imaging (MRI) scans and 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 marrow biopsy. Lyme disease (Chap. 210) 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 clinical 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 must be excluded (Chap. 432e). These are readily identified by appropriate laboratory tests. 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 examination 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 progressive weakness, atrophy, and fasciculations. Its cause is unknown, but it is thought to reflect sublethal prior injury to motor neurons by poliovirus (Chap. 228).

Rarely, ALS develops concurrently with features indicative of more widespread neurodegeneration. Thus, one infrequently encounters otherwise typical ALS patients with a parkinsonian movement disorder or frontotemporal dementia, particularly in instances of C9orf72 mutations, which strongly suggests that the simultaneous occurrence of two disorders is a direct consequence of the gene mutation. As another example, 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 brain (Chap. 448). In other cases, ALS develops simultaneously with a striking frontotemporal dementia. An ALS-like disorder has also been described in some individuals with chronic traumatic encephalopathy, associated with deposition of TDP43 and neurofibrillary tangles in motor neurons.

PATHOGENESIS

The cause of sporadic ALS is not well defined. Several mechanisms that impair motor neuron viability have been elucidated in mice and rats induced to develop motor neuron disease by SOD1 transgenes with ALS-associated mutations. One may loosely group the genetic causes of ALS into three categories. In one group, the primarily problem is inherent instability of the mutant proteins, with subsequent perturbations in protein degradation (SOD1, ubiquilin-1 and -2, p62). In the second, most rapidly growing category, the causative mutant genes perturb RNA processing, transport, and metabolism (C9orf73, TDP43, FUS). In the case of C9orf72, the molecular pathology is an expansion of an intronic hexanucleotide repeat (-GGGGCC-) beyond an upper normal of 30 repeats to hundreds or more repeats. As observed in other intronic repeat disorders such as myotonic dystrophy (Chap. 462e) and spinocerebellar atrophy type 8 (Chap. 450), data suggest that the expanded intronic repeats generate expanded RNA repeats that form intranuclear foci and confer toxicity by sequestering transcription factors or by undergoing noncanonical protein translation across all possible reading frames of the expanded RNA tracts. 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,