# 452 Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases

Robert H. Brown, Jr.

## AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is the most common form of progressive motor neuron disease. It is a prime example of a neurodegenerative disease and is arguably the most devastating of the neurodegenerative 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. 30). Although at its onset ALS may involve selective 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. 448); 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 452-1 and 452-2). Thus, in bulbar palsy and spinal muscular atrophy (SMA; also called *progressive muscular atrophy*), the lower motor neurons of brainstem and spinal cord, respectively, are most severely involved. By contrast, pseudobulbar palsy, primary lateral sclerosis (PLS), and familial spastic paraplegia (FSP) 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; ultrastructurally, these "spheroids" are composed of accumulations of neurofilaments and other proteins. Commonly in both sporadic and familial

**TABLE 452-1 ETIOLOGY OF MOTOR NEURON DISORDERS**

| Diagnostic Category | Investigation |
|---|---|
| Structural lesions | MRI scan of head (including foramen magnum and cervical spine) |
| Parasagittal or foramen magnum tumors | |
| Cervical spondylosis | |
| Chiari malformation of syrinx | |
| Spinal cord arteriovenous malformation | |
| Infections | CSF exam, culture |
| Bacterial—tetanus, Lyme | Lyme titer |
| Viral—poliomyelitis, herpes zoster | Anti-viral antibody |
| Retroviral—myelopathy | HTLV-1 titers |
| Intoxications, physical agents | 24-h urine for heavy metals |
| Toxins—lead, aluminum, others | Serum lead level |
| Drugs—strychnine, phenytoin | |
| Electric short, x-irradiation | |
| Immunologic mechanisms | Complete blood count[a] |
| Plasma cell dyscrasias | Sedimentation rate[a] |
| Autoimmune polyradiculopathy | Total protein[a] |
| Motor neuropathy with conduction block | Anti-GM1 antibodies[a] |
| | Anti-Hu antibody |
| Paraneoplastic | MRI scan, bone marrow biopsy |
| Paracarcinomatous | |
| Metabolic | Fasting blood sugar[a] |
| Hypoglycemia | Routine chemistries including calcium[a] |
| Hyperparathyroidism | PTH |
| Hyperthyroidism | Thyroid function[a] |
| Deficiency of folate, vitamin $B_{12}$, vitamin E | Vitamin $B_{12}$, vitamin E, folate[a] |
| Malabsorption | Serum zinc, copper[a] |
| Deficiency of copper, zinc | 24-h stool fat, carotene, prothrombin time |
| Mitochondrial dysfunction | Fasting lactate, pyruvate, ammonia |
| | Consider mtDNA |
| Hyperlipidemia | Lipid electrophoresis |
| Hyperglycinuria | Urine and serum amino acids |
| | CSF amino acids |
| Hereditary disorders | WBC DNA for mutational analysis |
| Superoxide dismutase | |
| TDP43 | |
| FUS/TLS | |
| Androgen receptor defect (Kennedy's disease) | |
| Hexosaminidase deficiency | |
| Infantile a-glucosidase deficiency (Pompe's disease) | |

[a]Should 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.