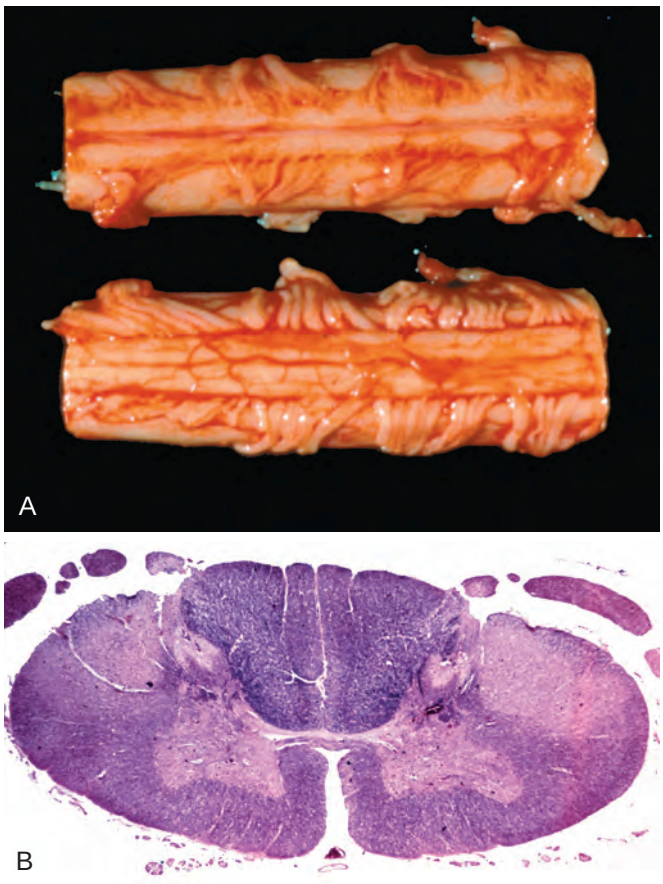

Figure 28-43 Amyotrophic lateral sclerosis. **A,** Segment of spinal cord viewed from anterior (upper) and posterior (lower) surfaces showing attenuation of anterior (motor) roots compared with posterior (sensory) roots. **B,** Spinal cord showing loss of myelinated fibers (lack of stain) in corticospinal tracts as well as degeneration of anterior roots.

also have evidence of more widespread cerebral cortical disease. The clinical presentation of cerebral disease is usually as a frontotemporal lobar dementia (FTLD), with pathologic findings most often matching those of FTLD associated with TDP-43 inclusions. The mechanistic link between these two processes is further strengthened by the presence of TDP-43 containing inclusions in many cases of ALS as well as partial sharing of genetic alterations in ALS and FTLD.

Other Motor Neuron Diseases

Spinal and Bulbar Muscular Atrophy (Kennedy Disease)

This X-linked polyglutamine repeat-expansion disease is characterized by distal limb amyotrophy and bulbar signs, such as atrophy and fasciculations of the tongue and dysphagia, associated with degeneration of lower motor neurons in the spinal cord and brainstem. The expanded repeat occurs in the first exon of the androgen receptor, and results in androgen insensitivity, gynecomastia, testicular atrophy, and oligospermia. The basis for the selective motor neuron involvement is unclear, but as in other polyglutamine expansion diseases such as Huntington disease and forms of spinocerebellar atrophy, there are intranuclear inclusions that contain the involved protein. Cellular injury depends on the binding of androgen to the abnormal receptor and the subsequent interaction with DNA. Therapies aimed at reducing androgen levels have been effective is animal models and may be able to ameliorate the disease in humans as well.

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) includes a group of genetically linked disorders of childhood with marked loss of lower motor neurons resulting in progressive weakness. The most severe form is that with the earliest onset (SMA type I, Werdnig-Hoffmann disease) with onset during the first year of life and death typically within 2 years. Other forms, with later onset, have more gradual courses; in SMA type III (Kugelberg-Welander disease) motor disability usually emerges during later childhood and adolescence. The severity of disease is related to the level of a protein (termed SMN) that is involved in the assembly of the spliceosome; there are decreased nuclear puncta containing SMN in cells from affected individuals. Most SMN protein comes from mRNA transcripts derived from the *SMN1* gene on chromosome 5q. There is an adjacent *SMN2* gene that differs by a few base pairs, including changes which decrease the efficiency of inclusion of one exon in the mRNA. SMN protein lacking this region is much less stable than the full-length protein. All of the forms of SMA are associated with disruption of *SMN1* (usually through deletion), with the differences in clinical phenotype determined by copy number variation for the *SMN2* gene. Methods of altering the splicing of *SMN2*-derived transcripts are being explored as novel therapeutic approaches for these diseases.

KEY CONCEPTS

Neurodegenerative Diseases

- Neurodegenerative diseases are characterized by progressive neuronal loss involving specific neuronal circuits and brain regions. Most of these diseases are associated with accumulation of abnormal protein aggregates, typically in the form of cellular inclusions. The clinical phenotype reflects the patterns of brain involvement more than the type of inclusions.
- These diseases can be grouped by clinical presentation into: dementias, hypokinetic movement disorders (including forms of parkinsonism), hyperkinetic movement disorders, cerebellar ataxias, and motor neuron diseases.
- Among dementias, AD (with plaques of Aβ and tangles of tau) is the most common; other predominantly dementing diseases include the various forms of FTLDs (both forms with tau-containing lesions and with other types of inclusions) and dementia with Lewy bodies (with α-synuclein containing lesions).
- Among the hypokinetic movement disorders, Parkinson disease is the most common, again with α-synuclein containing inclusions); others diseases which include parkinsonism as part of the symptoms, include PSP and CBD (both forms of tauopathy).
- Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease, with diverse genetic causes as well as sporadic forms.