example, glial cytoplasmic inclusions are consistently observed in the white matter projecting to and from the motor cortex. The origin of the α-synuclein in oligodendrocytes remains perplexing, since this is a neuronal protein associated with synaptic vesicles. Several studies have shown that there is no up-regulation of α-synuclein expression in white matter or in oligodendrocytes in MSA. It has been suggested that oligodendrocytes may acquire α-synuclein aggregates secondarily from injured or dying neurons. When α-synuclein is present in oligodendrocytes, they become more sensitive to oxidative stress and show impaired interaction with the extracellular matrix.

MORPHOLOGY

The pathologic findings in MSA match the clinical presentation in any particular case. In cerebellar forms there is atrophy of the cerebellum, including the cerebellar peduncles, pons (especially the basis pontis, Fig. 28-41*A*), and medulla (especially the inferior olive), while in parkinsonian forms the atrophy involves both the substantia nigra and striatum (especially putamen). Autonomic symptoms are related to cell loss from the catecholaminergic nuclei of the medulla and the intermediolateral cell column of the spinal cord. Atrophic brain regions show evidence of neuronal loss as well as variable numbers of neuronal cytoplasmic and nuclear inclusions.

The diagnostic glial cytoplasmic inclusions were originally demonstrated in oligodendrocytes with silver impregnation methods and contain α-synuclein as well as ubiquitin (Fig. 28-41*B*). The inclusions are ultrastructurally distinct from those found in other neurodegenerative diseases and are composed primarily of 20- to 40-nm tubules. Similar inclusions may also be found in the cytoplasm of neurons, sometimes in neuronal and glial nuclei, and in axons.

Huntington Disease

Huntington disease (HD) is an autosomal dominant disease characterized by progressive movement disorders and dementia, caused by degeneration of striatal neurons. Jerky, hyperkinetic, sometimes dystonic movements involving all parts of the body (chorea) are characteristic; affected individuals may later develop bradykinesia and rigidity. The disease is relentlessly progressive and uniformly fatal, with an average course of about 15 years.

Molecular Genetics and Pathogenesis. **HD is the prototype of the polyglutamine trinucleotide repeat expansion diseases** (Chapter 5). The gene for HD, *HTT*, located on chromosome 4p16.3, encodes a 348-kD protein known as *huntingtin*. In the first exon of the gene there is a stretch of CAG repeats that encodes a polyglutamine region near the N terminus of the protein. Normal *HTT* genes contain six to 35 copies of the repeat; when the number of repeats is increased beyond this level it is associated with disease. There is an inverse relationship between repeat number and age of onset, such that longer repeats tend to be associated with earlier onset. However, determination of repeat length is not by itself an accurate predictor of age of onset. Repeat expansions occur during spermatogenesis, so that paternal transmission is associated with early onset in the next generation, a phenomenon termed *anticipation*. In contrast to many of the other degenerative diseases, there is no sporadic form of HD. Newly occurring mutations are uncommon; most apparently sporadic cases are explained by non-paternity, the death of a parent before the disease is expressed, or an unaffected father with a mild repeat expansion that is expanded to a pathogenic size during spermatogenesis.

The biologic function of normal huntingtin remains unknown, but it appears that the expansion of the polyglutamine region bestows a toxic gain-of-function on huntingtin. For this reason, various approaches to silencing expression of the mutant allele are being investigated as potential therapies. It is interesting to note that while huntingtin is expressed in all the tissues of the body, the deleterious effects of mutant huntingtin occur only in selected parts of the central nervous system.

While protein aggregation and development of intranuclear inclusions containing huntingtin are pathologic hallmarks of HD, it remains uncertain whether these processes are directly involved in cellular injury or if they are incidental to critical disease processes. There is emerging evidence that aggregated huntingtin can be taken up by neurons, again suggesting a prion-like spread from one

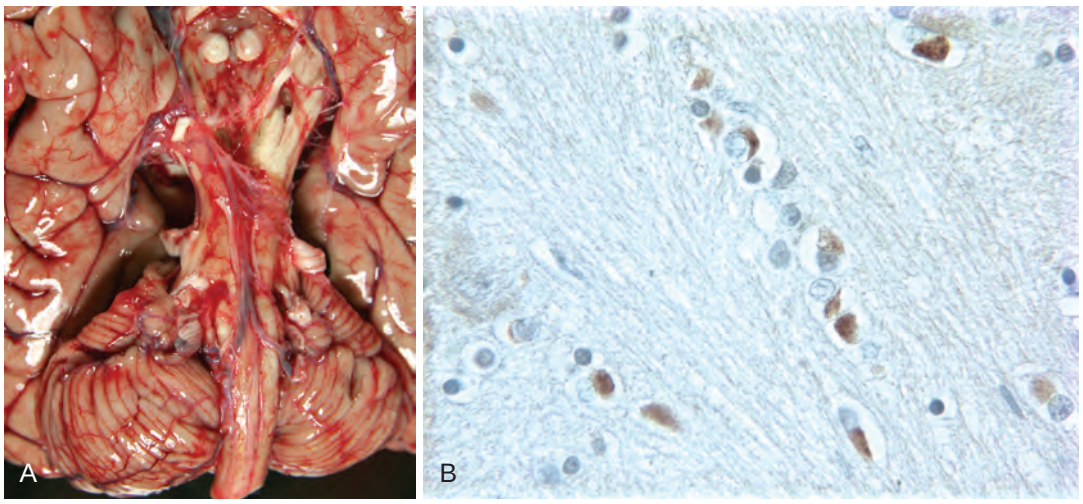

Figure 28-41 Multiple system atrophy (MSA). **A,** Severe atrophy of the basis pontis is evidence in a case of MSA-C. **B,** Inclusions in oligodendrocytes contain α-synuclein.