predominantly of α-synuclein. Immunohistochemical staining for α-synuclein also reveals the presence of abnormal neurites, that contain aggregated protein—called *Lewy neurites,* even though Lewy never saw them! In this setting, the pathologic findings typically include depigmentation of the substantia nigra and locus ceruleus, paired with relative preservation of the cortex, hippocampus, and amygdala. The burden of cortical Lewy bodies is usually extremely low, and the mechanism by which this disease wreaks havoc on cognitive functioning is not clear. There is evidence that the burden of oligomeric α-synuclein in the cortex is more important than the Lewy bodies, even though neuropathologists use the latter as the diagnostic hallmark of the disease.

Atypical Parkinsonism Syndromes

As discussed earlier, the clinical syndrome of parkinsonism, with bradykinesia and rigidity, reflects dysfunction of the extrapyramidal circuitry, particularly the dopaminergic nigrostriatal projection. In addition to the forms of Parkinson disease already discussed, there are a variety of disorders which include parkinsonism as a component of the symptoms. These diseases, in general, are minimally responsive to treatment with L-DOPA; they are also distinguished from Parkinson disease through the presence of additional signs and symptoms. For these reasons, they are considered to be "atypical parkinsonism syndromes," with the alternative terminology of "Parkinson-plus syndromes" applied by others. In addition to progressive supranuclear palsy and corticobasal degeneration, which are both tauopathies, another synucleinopathy (multisystem atrophy, discussed separately later) is also in this group of disorders.

Progressive Supranuclear Palsy (PSP)

PSP is a tauopathy in that affected individuals commonly develop progressive truncal rigidity, disequilibrium with frequent falls and difficulty with voluntary eye movements. Other symptoms that are frequently observed include nuchal dystonia, pseudobulbar palsy and a mild progressive dementia. The onset is usually between the fifth and seventh decades, with males affected approximately twice as frequently as females. The disease is often fatal within 5 to 7 years of onset.

Although the pathologic hallmark of PSP is the presence of tau-containing inclusions in neurons and glia, causative mutations in the tau gene have been identified in only a few cases. However, risk for sporadic PSP is linked to single nucleotide polymorphisms that map near the tau gene locus. Other risk alleles have been identified through genome-wide association studies, but the mechanisms by which they influence development of PSP are still unclear.

MORPHOLOGY

There is widespread neuronal loss in the globus pallidus, subthalamic nucleus, substantia nigra, colliculi, periaqueductal gray matter, and dentate nucleus of the cerebellum. Globose fibrillary tangles are found in these affected regions, in neurons as well as in glia. Ultrastructural analysis reveals 15-nm straight filaments that are composed of 4R tau.

Corticobasal Degeneration (CBD)

CBD is a progressive tauopathy that is most often characterized by extrapyramidal rigidity, asymmetric motor disturbances (jerking movements of limbs), and impaired higher cortical function (typically in the form of apraxias). As with PSP, cognitive decline may occur, typically later in the illness. The same tau variant linked to PSP is also highly associated with CBD. Overall, CBD and PSP share many clinical and pathologic features; in general, with PSP there is a greater burden of tau-containing lesions in brainstem and deep gray matter, while in CBD the balance is shifted more toward cerebral cortical involvement.

MORPHOLOGY

The brain shows cortical atrophy, mainly of the motor, premotor, and anterior parietal lobes. In affected regions of cortex there is severe loss of neurons, gliosis, and **"ballooned" neurons** (neuronal achromasia). Tau immunoreactivity has been found in astrocytes ("tufted astrocytes"), oligodendrocytes ("coiled bodies"), basal ganglionic neurons, and, variably, cortical neurons. Clusters of tau-positive processes around astrocytes ("astrocytic plaques") and the presence of tau-positive threads in gray and white matter may be the most specific pathologic findings of CBD. The substantia nigra and locus ceruleus show loss of pigmented neurons, neuronal achromasia, and tangles.

Multiple System Atrophy (MSA)

MSA is a sporadic disorder that affects several functional systems in the brain and is characterized by cytoplasmic inclusions of α-synuclein in oligodendrocytes. Unlike the other degenerative diseases, the primary pathologic hallmark of MSA is observed in glial cells and is commonly associated with degeneration of white matter tracts. In addition, there is accompanying neuronal degeneration but typically without the presence of inclusions. The "multiple" in the term *multiple system atrophy* refers to three distinct neuroanatomic circuits that are commonly involved: the striatonigral circuit (leading to parkinsonism), olivopontocerebellar circuit (leading to ataxia), and the autonomic nervous system including the central elements (leading to autonomic dysfunction, with orthostatic hypotension as a prominent component). In a given individual, one of these components may predominate at the onset of the illness, but typically the other systems are affected as MSA progresses.

Pathogenesis. As in Parkinson disease, α-synuclein is the major component of the inclusions. MSA is a sporadic disease and no mutations in the gene encoding α-synuclein have identified as being causative; nonetheless, there does appear to be a set of polymorphisms near this gene that confer increased risk. The relationship between glial cytoplasmic inclusions and disease is supported by the observation that the burden of inclusions increases as the disease progresses, although inclusions eventually disappear as cells die in the final stages. It appears that glial cytoplasmic inclusions can occur in the absence of neuronal loss, suggesting that they are the primary pathologic event; for