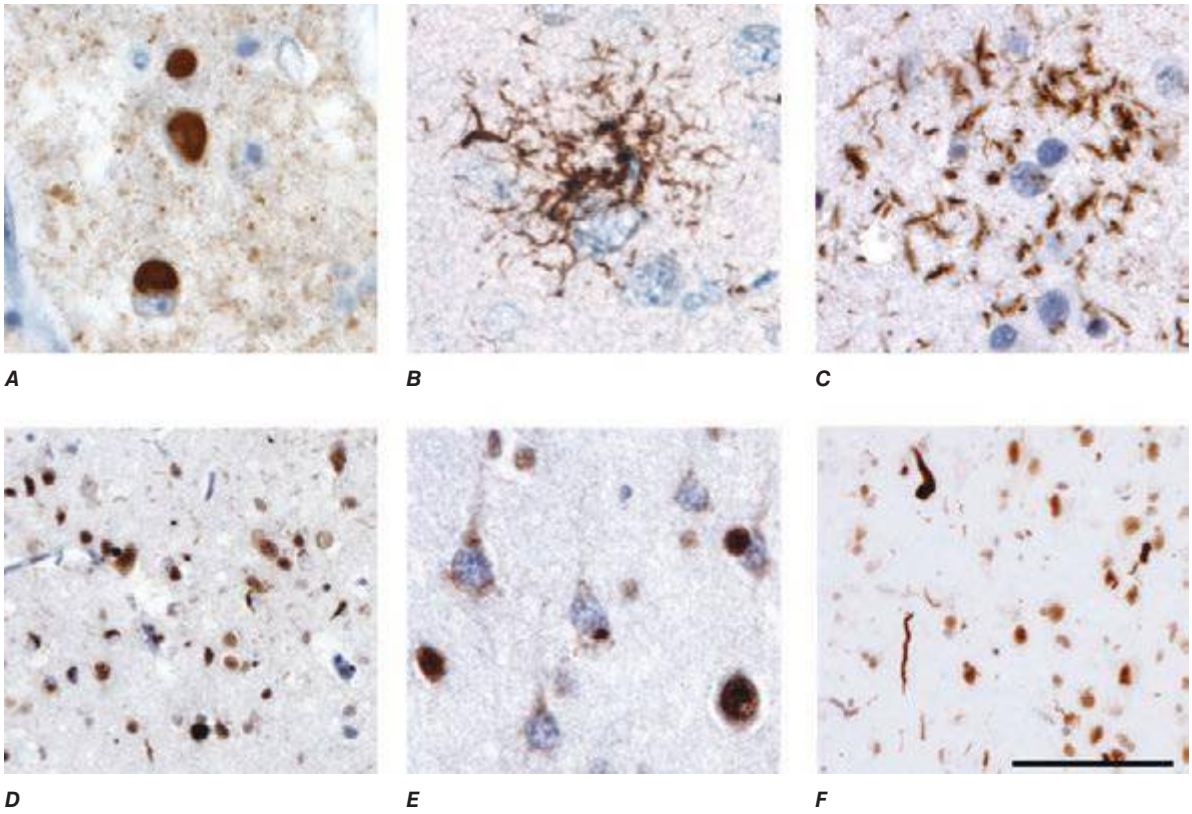

FIGURE 448-5 Neuropathology in frontotemporal lobar degeneration (FTLD). FTLD-tau (***A–C***) and FTLD-TDP (***D–F***) account for over 90% of patients with FTLD, and immunohistochemistry reveals characteristic lesions in each of the major histopathologic subtypes within each class: (***A***) Pick bodies in Pick's disease; (***B***) a tufted astrocyte in progressive supranuclear palsy; (***C***) an astrocytic plaque in corticobasal degeneration; (***D***) small compact or crescentic neuronal cytoplasmic inclusions and short, then neuropil threads in FTLD-TDP, type A; (***E***) diffuse/granular neuronal cytoplasmic inclusions (with a relative paucity of neuropil threads) in FTLD-TDP, type B; and (***F***) long, tortuous dystrophic neurites in FTLD-TDP, type C. TDP can be seen within the nucleus in neurons lacking inclusions but mislocalizes to the cytoplasm and forms inclusions in FTLD-TDP. Immunostains are 3-repeat tau (***A***), phospho-tau (***B*** and ***C***), and TDP-43 (***D–F***). Sections are counterstained with hematoxylin. Scale bar applies to all panels and represents 50 μm in ***A***, ***B***, ***C***, and ***E*** and 100 μm in ***D*** and ***F***.

be large, spherical ("globose"), and coarse in brainstem, cerebellar dentate, and diencephalic neurons. Tau deposition is most prominent in subcortical structures (including the subthalamic nucleus, globus pallidus, substantia nigra, locus coeruleus, periaqueductal gray, tectum, oculomotor nuclei, and dentate nucleus of cerebellum). Neocortical NFTs, like those in AD, often take on a more flame-shaped morphology, but on electron microscopy, PSP tangles can be shown to consist of straight tubules rather than the paired helical filaments found in AD. Furthermore, PSP is associated with prominent tau-positive glial pathologies, such as tufted astrocytes (Fig. 448-5), thorny astrocytes, and coiled oligodendroglial inclusions ("coiled bodies"). Most patients with PSP-S show PSP at autopsy, although small numbers will show another tauopathy (corticobasal degeneration [CBD] or Pick's disease; Fig. 448-4).

In addition to its overlap with FTD and CBS (see below), PSP is often confused with idiopathic *Parkinson's disease* (PD). Although elderly patients with PD may have restricted upgaze, they do not develop downgaze paresis or other abnormalities of voluntary eye movements typical of PSP. Dementia occurs in ~20% of patients with PD, often due to the emergence of a full-blown DLB-like syndrome. Furthermore, the behavioral syndromes seen with DLB differ from PSP (see below). Dementia in PD becomes more likely with increasing age, increasing severity of extrapyramidal signs, long disease duration, and the presence of depression. Patients with PD who develop dementia also show cortical atrophy on brain imaging. Neuropathologically, there may be AD-related changes in the cortex, LBD-related α-synuclein inclusions in both the limbic system and cortex, or no specific microscopic changes other than gliosis and neuronal loss. **PD is discussed in detail in Chap. 449.**

Corticobasal syndrome (CBS) is a slowly progressive dementia-movement disorder associated with severe atrophy in perirolandic cortex and basal ganglia (substantia nigra and striatopallidum). Patients typically present with asymmetric onset of rigidity, dystonia, myoclonus, and apraxia of one limb, at times associated with *alien limb* phenomena in which the limb exhibits unintended motor actions such as grasping, groping, drifting, or undoing. Eventually CBS becomes bilateral and leads to dysarthria, slow gait, action tremor, and typically a frontal-predominant dementia. Whereas CBS refers to the clinical syndrome, CBD refers to a specific histopathologic FTLD-tau entity (Fig. 448-4). Although CBS was once thought to be pathognomonic for CBD, increasingly it has been recognize that CBS can be due to CBD, PSP, FTLD-TDP, or even AD. In CBD, the microscopic features include ballooned, achromatic, tau-positive neurons; astrocytic plaques (Fig. 448-5); and other dystrophic glial tau pathomorphologies that overlap with those seen in PSP. Most specifically, CBD features a severe tauopathy burden in the subcortical white matter, consisting of threads and oligodendroglial coiled bodies. As shown in Fig. 448-4, patients with bvFTD, nonfluent/agrammatic PPA, and PSP-S may also show CBD at autopsy, emphasizing the importance of distinguishing clinical and pathologic constructs and terminology. Treatment of CBS remains symptomatic; no disease-modifying therapies are available.

PARKINSON'S DISEASE DEMENTIA AND DEMENTIA WITH LEWY BODIES

The parkinsonian dementia syndromes are under increasing study, with many cases unified by Lewy body and Lewy neurite pathology that ascends from the low brainstem up through the substantia nigra,