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Neuropathology of Parkinsonism

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INTRODUCTION

The common denominator of virtually all disorders associated with clinical parkinsonism is neuronal loss in the substantia nigra, particularly of dopaminergic neurons in the pars compacta that project to the striatum (Fig. 1). The ventrolateral tier of neurons appears to be the most vulnerable in many parkinsonian disorders, and these tend to project heavily to the putamen (1). The more medial groups of neurons send projections to forebrain and medial temporal lobe and are less affected. The dorsal tier of neurons may be most vulnerable to neuronal loss associated with aging (1).

PARKINSON'S DISEASE

The clinical features of Parkinson's disease (PD) include bradykinesia, rigidity, tremor, postural instability, autonomic dysfunction, and brady-phrenia. The most frequent pathological substrate for PD is Lewy body disease (LBD) (2). Some cases of otherwise clinically typical PD have other disorders, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), or vascular disease, but these are uncommon, especially
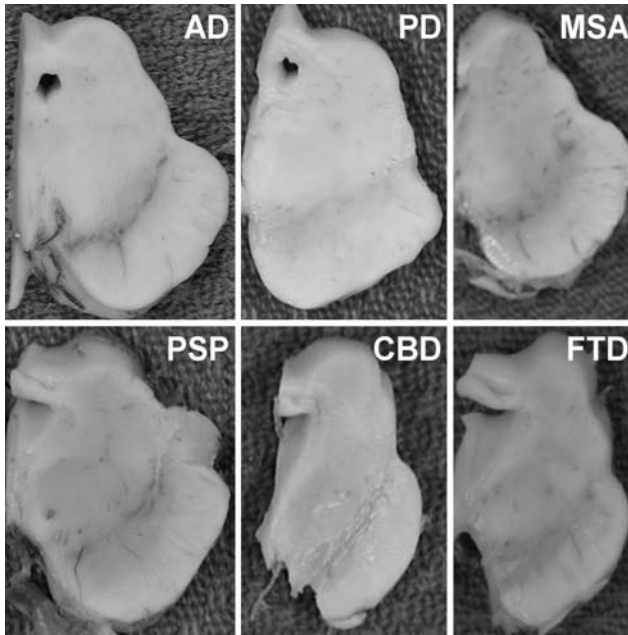
FIGURE 1 Midbrain sections from a variety of disorders associated with Parkinsonism, including Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and frontotemporal dementia (FTD) and a disorder not associated with parkinsonism, Alzheimer's disease (AD). Note loss of pigment in the substantia nigra in all disorders except AD.

when the clinical diagnosis is made after several years of clinical follow-up (3,4). The diagnostic accuracy rate approached 90% in some recent series (5).

The brain is usually grossly normal when viewed from the outer surface. There may be mild frontal atrophy is some cases, but this is variable. The most obvious morphological change in PD is only visible after the brainstem is sectioned. The loss of neuromelanin pigmentation in the substantia nigra and locus ceruleus is usually grossly apparent and may be associated with a rust color in the pars reticulata, which correlates with increased iron deposition in the tissue. Histologically, there is neuronal loss in the substantia nigra pars compacta along with compensatory astrocytic and microglial proliferation. While biochemically there is loss of dopaminergic termini in the striatum, the striatum is histologically unremarkable. In the substantia nigra and locus ceruleus neuromelanin pigment may be

found in the cytoplasm of macrophages. Less common are neurons undergoing neuronophagia (i.e., phagocytosis by macrophages). Hyaline cytoplasmic inclusions, so-called Lewy bodies (LBs), and less well-defined "pale bodies" are found in some of the residual neurons in the substantia nigra (Fig. 2). Similar pathology is found in the locus ceruleus, the dorsal motor nucleus of the vagus, as well as the basal forebrain (especially the basal nucleus of Meynert). The convexity neocortex usually does not have LBs, but the limbic cortex and the amygdala may be affected. Depending upon the age of the individual, varying degrees of Alzheimer type pathology may be detected, but if the person is not demented, this usually falls within the limits for that age. Some cases may have abundant senile plaques but few or no neurofibrillary tangles.

Lewy bodies are proteinaceous neuronal cytoplasmic inclusions (reviewed in Refs. 6 and 7). In some regions of the brain, such as the dorsal motor nucleus of the vagus, LBs tend to form within neuronal processes and are sometimes referred to as intraneuritic LBs. In most cases LBs are accompanied by a variable number of abnormal neuritic profiles, referred to as Lewy neurites. Lewy neurites were first described in the hippocampus (8), but they are also found in other regions of the brain, including the amygdala, cingulate gyrus, and temporal cortex. At the electron microscopic level, LBs are composed of densely aggregated
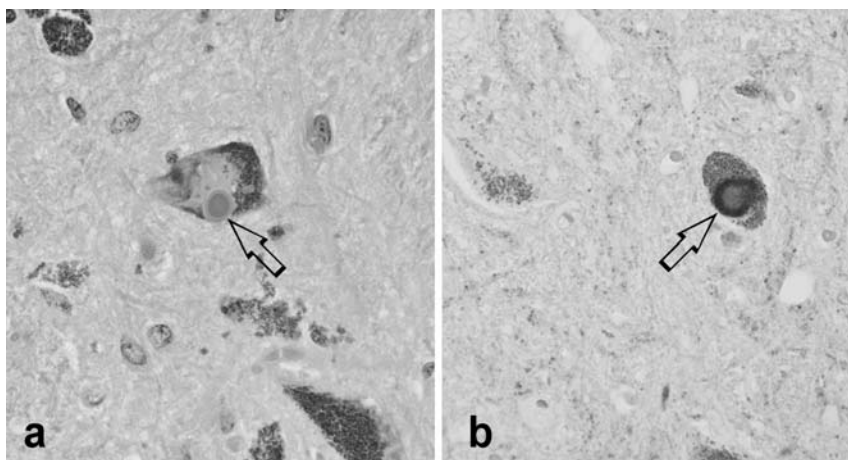

FIGURE 2 PD: Lewy bodies are hyaline inclusions visible with routine histological methods in pigmented neurons of the substantia nigra (arrow in a). They are immunostained with antibodies to synuclein (arrow in b).

filaments (9), and Lewy neurites also are filamentous, but they are usually not as densely packed (8).

Neurons that are most vulnerable to LBs include the monoaminergic neurons of the substantia nigra, locus ceruleus, and dorsal motor nucleus of the vagus, as well as cholinergic neurons in the basal forebrain. LBs are rarely detected in the basal ganglia or thalamus, but are common in the hypothalamus, especially the posterior and lateral hypothalamus, and the brainstem reticular formation. The oculomotor nuclear complex is also vulnerable. In the pons, the dorsal raphe and subpeduncular nuclei are often affected, but neurons of the pontine base are not. LBs have not been described in the cerebellar cortex. In the spinal cord, the neurons of the intermediolateral cell column are most vulnerable. LBs can be found in the autonomic ganglia, including submucosal ganglia of the esophagus.

While not usually numerous in typical PD, LBs can be found in cortical neurons, especially in the limbic lobe. Cortical LBs can be difficult to detect with routine histology, but they are visible with special staining techniques and are usually most numerous in small nonpyramidal neurons in lower cortical layers. Similar lesions in the substantia nigra are referred to as "pale bodies" or as "pre-Lewy bodies." Ultrastructural studies of cortical LBs demonstrate poorly organized filamentous structures similar to Lewy neurites.

The chemical composition of LBs has been inferred from immuno-histochemical studies. While antibodies to neurofilament were first shown to label LBs (10), ubiquitin (11) and more recently α-synuclein (12) (Fig. 2) antibodies are better markers for LBs, and α-synuclein appears to be the most specific marker currently available. Lewy neurites have the same immunoreactivity profile as LBs (13). Biochemical studies of purified LBs have not been accomplished, but evidence suggests that they may contain a mixture of proteins including neurofilament and α-synuclein (14–16).

DEMENTIA IN PD

Pathological findings considered to account for dementia in PD include severe pathology in monoaminergic and cholinergic nuclei that project to the cortex producing a "subcortical dementia" (39%), coexistent Alzheimer's disease (AD) (29%) and diffuse cortical LBs (26%) (17). The basal forebrain cholinergic system is the subcortical region most often implicated in dementia, and neurons in this region are damaged in both AD and LBD. Neuronal loss in the basal nucleus is consistently found in PD, especially PD with dementia (18). Cholinergic deficits are common in PD (19), and they may contribute to dementia in PD in those cases that do not have concurrent AD or cortical LBs.

While virtually all PD brains have a few cortical LBs (17), they are usually neither widespread nor numerous in PD patients who are not demented. Several recent studies have shown, however, that cortical LBs are numerous and widespread in PD with dementia (20–22) and that the density of cortical LBs and Lewy neurites, especially in the medial temporal lobe (23), correlates with the severity of dementia (24).

MULTIPLE SYSTEM ATROPHY

The term multiple system atrophy refers to a neurodegenerative disease characterized by parkinsonism, cerebellar ataxia, and autonomic dysfunction (25). The average age of onset is between 30 and 50 years, and the disease duration runs in the decades (25). There is no known genetic risk factor or genetic locus for MSA. The MSA brain shows varying degrees of atrophy of cerebellum, cerebellar peduncles, pons and medulla, as well as atrophy and discoloration of the posterolateral putamen and pigment loss in the substantia nigra. The histopathological findings include neuronal loss, gliosis, and microvacuolation, involving the putamen, substantia nigra, cerebellum, olivary nucleus, pontine base, and intermediolateral cell column of the spinal cord. White matter inevitably shows demyelination, with the brunt of the changes affecting white matter tracts in cerebellum and pons (Fig. 3).

Lantos and coworkers first described oligodendroglial inclusions in MSA and named them glial cytoplasmic inclusions (GCIs) (26). GCIs can be detected with silver stains, such as the Gallyas silver stain, but are best seen with antibodies to synuclein, where they appear as flame- or sickle-shaped inclusions in oligodendrocytes (Fig. 3). Like LBs, GCIs are also immunostained with antibodies to ubiquitin (26). At the ultrastructural level, GCIs are non–membrane-bound cytoplasmic inclusions composed of filaments (7–10 nm) and granular material that often coats the filaments, making precise measurements difficult (27). GCIs are specific for MSA and have not been found in other neurodegenerative diseases. In addition to GCIs, synuclein immunoreactive lesions are also detected in some neurons in MSA. Biochemical studies of synuclein in MSA have shown changes in its solubility (27).

NEUROPATHOLOGY OF PROGRESSIVE SUPRANUCLEAR PALSY

PSP, an atypical parkinsonian disorder associated with progressive axial rigidity, vertical gaze palsy, dysarthria, and dysphagia, was first described by Steele-Richardson-Olszewski (28). Frontal lobe syndrome and subcortical
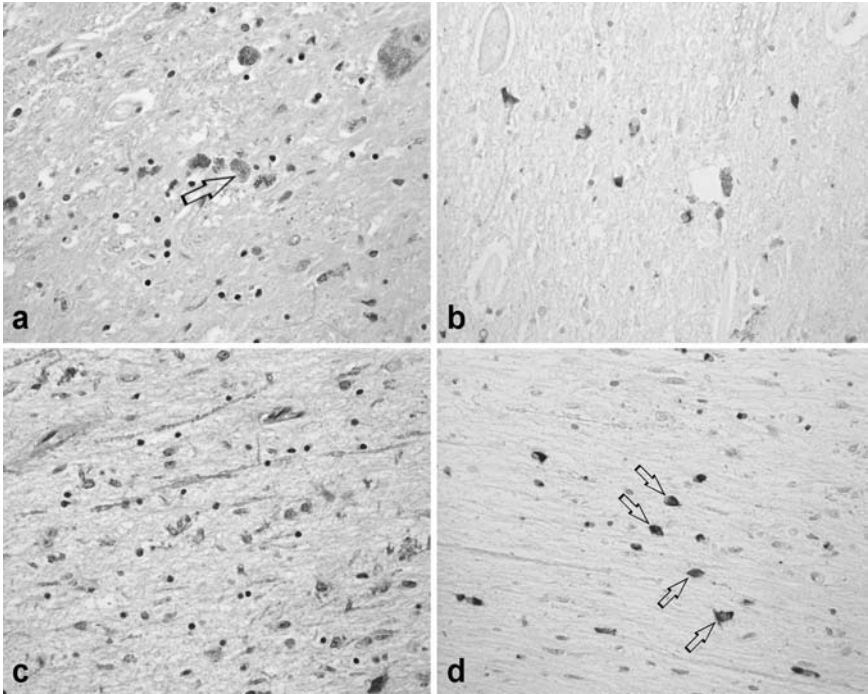
FIGURE 3 MSA: Substantia nigra neuronal loss in MSA is obvious in the cluster of pigment-laden macrophages (arrow in a), but neuronal inclusions are not present. Synuclein immunostaining of the substantia nigra shows many small inclusions in oligodendroglial cells (b). The white matter in the cerebellum shows marked myelin loss (Luxol fast blue stain for myelin) (c), and in the affected areas there are many synuclein-immunoreactive glial inclusions (arrows) (d).

dementia are present in some cases. In contrast to PD, gross examination of the brain often has distinctive features. Most cases have varying degrees of frontal atrophy that may involve the precentral gyrus. The midbrain, especially the midbrain tectum, and to a lesser extent the pons shows atrophy. The third ventricle and aqueduct of Sylvius may be dilated. The substantia nigra shows loss of pigment, while the locus ceruleus is often better preserved. The subthalamic nucleus is smaller than expected and may have a gray discoloration. The superior cerebellar peduncle and the hilus of the cerebellar dentate nucleus are usually atrophic and have a gray color due to myelinated fiber loss.

Microscopic findings include neuronal loss, gliosis, and neurofibrillary tangles (NFTs) affecting basal ganglia, diencephalon, and brainstem (Fig. 4). The nuclei most affected are the globus pallidus, subthalamic nucleus,
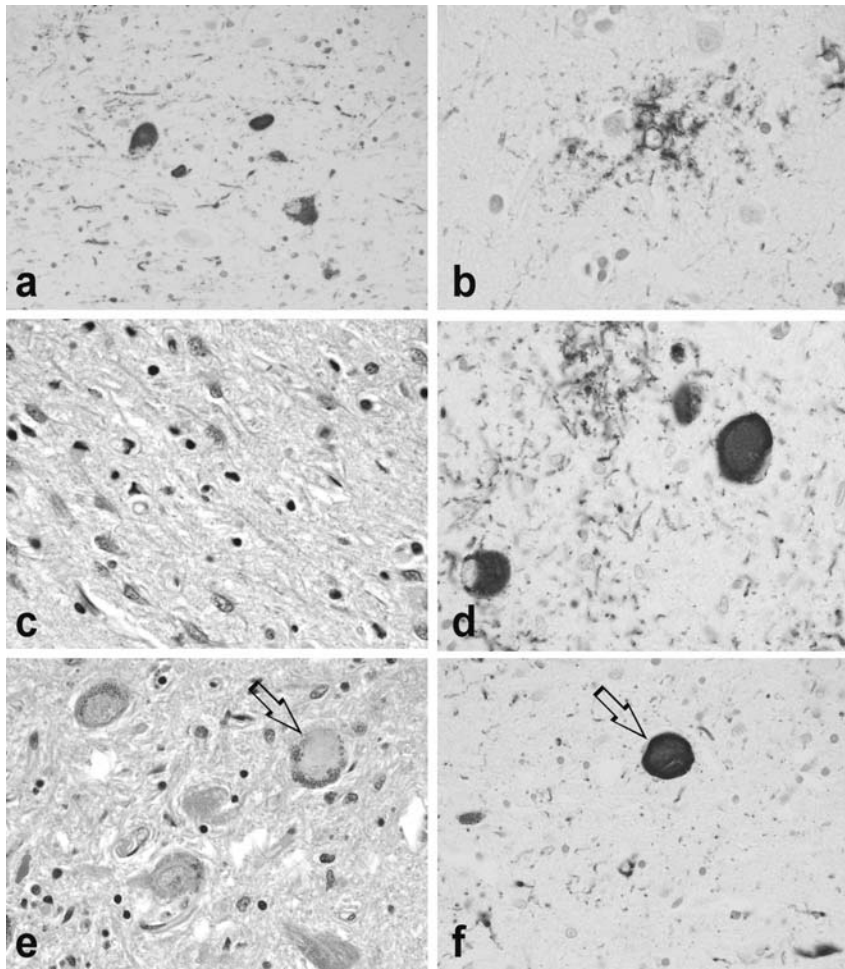

FIGURE 4 PSP: The basal ganglia have NFTs and threads (a) and tufted astrocytes (b) with tau immunostains. There is severe neuronal loss and gliosis in the subthalamic nucleus (c) and many NFT and glial lesions in the subthalamic nucleus (d). The substantia nigra has neuronal loss and NFTs in pigmented neurons (arrow) (e). The neurons in the substantia nigra have tau-immunoreactive NFTs (f).

and substantia nigra. The cerebral cortex is relatively spared, but lesions are common in the peri-Rolandic region. Recent studies suggest that cortical pathology may be more widespread in cases of PSP with atypical features, such as dementia (29). The limbic lobe is preserved in PSP.

The striatum and thalamus often have some degree of neuronal loss and gliosis, especially ventral anterior and lateral thalamic nuclei. The basal nucleus of Meynert usually has mild cell loss. The brainstem regions that are affected include the superior colliculus, periaqueductal gray matter, oculomotor nuclei, locus ceruleus, pontine nuclei, pontine tegmentum, vestibular nuclei, medullary tegmentum, and inferior olives. The cerebellar dentate nucleus is frequently affected and may show grumose degeneration, a type of neuronal degeneration associated with clusters of degenerating presynaptic terminals around dentate neurons. The dentatorubrothalamic pathway consistently shows fiber loss. The cerebellar cortex is preserved, but there may be mild Purkinje cell loss with scattered axonal torpedoes. The spinal cord is often affected, where neuronal inclusions can be found in anterior horn and intermediolateral cells.

Silver stains (e.g., Gallyas stain) or immunostaining for tau reveal NFTs in residual neurons in the basal ganglia, diencephalon, brainstem, and spinal cord. In addition to NFTs, special stains demonstrate argyrophilic, tau-positive inclusions in both astrocytes and oligodendrocytes. Tufted astrocytes are increasingly recognized as a characteristic feature of PSP and are commonly found in motor cortex and striatum (30) (Fig. 4). They are fibrillary lesions within astrocytes based upon double immunolabeling of tau and glial fibrillary acidic protein. Oligodendroglial lesions appear as argyrophilic and tau-positive perinuclear fibers, so-called coiled bodies, and they are often accompanied by thread-like processes in the white matter, especially in the diencephalon and cerebellar white matter.

NFTs in PSP are composed of 15 nm straight filaments (31). The abnormal filaments in glial cells in PSP also contain straight filaments. Biochemical studies also show differences between tau in AD and PSP. In AD the abnormal insoluble tau migrates as three major bands (68, 64, and 60 kDa) on Western blots, while in PSP it migrates as two bands (68 and 64 kDa) (32).

CORTICOBASAL DEGENERATION

Corticobasal degeneration (CBD) is only rarely mistaken for PD due to characteristic focal cortical signs that are the clinical hallmark of this disorder. Common clinical presentations include progressive asymmetrical rigidity and apraxia, progressive aphasia, and progressive frontal lobe dementia (33). Most cases also have some degree of parkinsonism, with

bradykinesia, rigidity, and dystonia more common than tremor. Given the prominent cortical findings on clinical evaluations, it is not surprising that gross examination of the brain often reveals focal cortical atrophy. The atrophy may be severe and "knife-edge" in some cases or subtle and hardly noticeable in others. It may be asymmetrical. Atrophy is often most marked in the medial superior frontal gyrus, parasagittal pre- and postcentral gyri, and the superior parietal lobule. The temporal and occipital lobes are usually preserved. The brainstem does not have gross atrophy as in PSP, but pigment loss is common in the substantia nigra. In contrast to PSP, the superior cerebellar peduncle and the subthalamic nucleus are grossly normal.
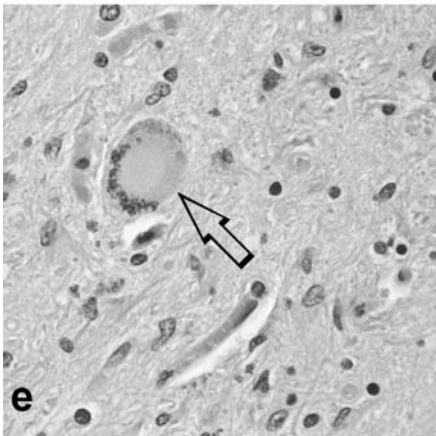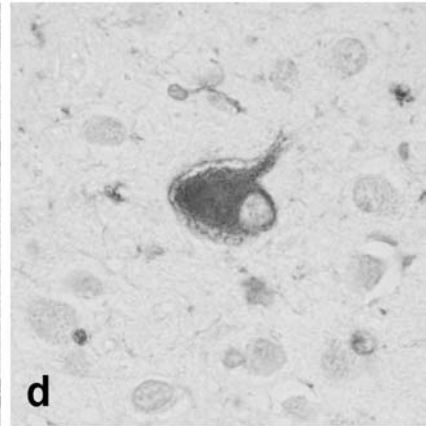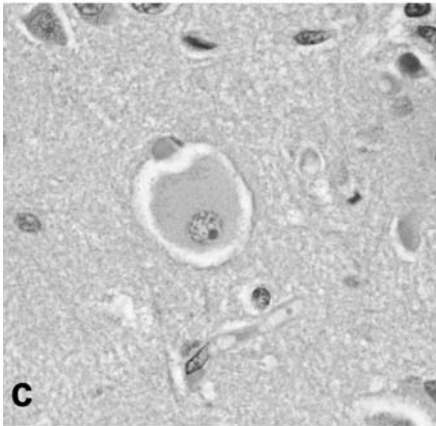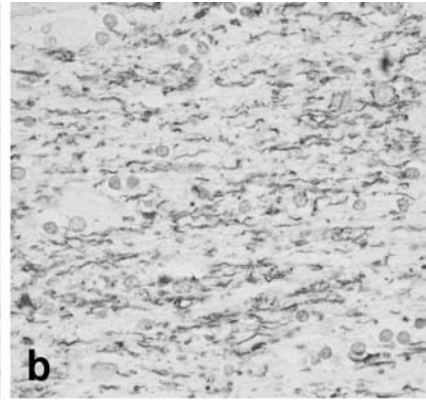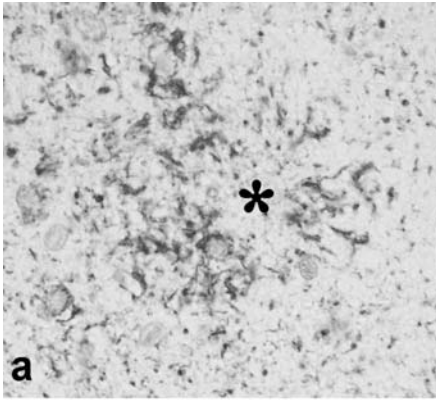
The cerebral white matter in affected areas is often attenuated and may have a gray discoloration. The corpus callosum is sometimes thinned, and the frontal horn of the lateral ventricle is frequently dilated. The caudate head may have flattening. The thalamus may be smaller than usual.

Microscopic examination of atrophic cortical sections shows neuronal loss with superficial spongiosis, gliosis, and usually many achromatic or ballooned neurons. Ballooned neurons are swollen and vacuolated neurons found in the middle and lower cortical layers. They are variably positive with silver stains and tau immunohistochemistry, but intensely stained with immunohistochemistry for alpha-B-crystallin, a small heat shock protein, and for neurofilament (Fig. 5).

Cortical neurons in atrophic areas also have tau-immunoreactive lesions. In some neurons tau is densely packed into a small inclusion body, somewhat reminiscent of a Pick body or a small NFT. In other neurons, the filamentous inclusions are more dispersed and diffuse. As in PSP, neurofibrillary lesions in CBD are not detected well with most diagnostic silver stains and thioflavin fluorescent microscopy. Neurofibrillary lesions in brainstem monoaminergic nuclei, such as the locus ceruleus and substantia nigra, sometimes resemble globose NFT.

In addition to fibrillary lesions in perikarya of neurons, the neuropil of CBD invariably contains a large number of thread-like tau-immunoreactive processes. They are usually profuse in both gray and white matter, and this latter feature is an important attribute of CBD and a useful feature in differentiating it from other disorders (34).

The most characteristic tau-immunoreactive lesion in the cortex in CBD is an annular cluster of short, stubby processes with fuzzy outlines that may be highly suggestive of a neuritic plaque of AD (34) (Fig. 5). In contrast to AD plaques, they do not contain amyloid but rather tau-positive astrocytes and have been referred to as "astrocytic plaques." Astrocytic plaques differ from the tufted astrocytes seen in PSP, and the two lesions do

not coexist in the same brain (30). The astrocytic plaque may be the most specific histopathological lesion of CBD.

In addition to cortical pathology, deep gray matter is consistently affected in CBD. The globus pallidus and putamen show mild neuronal loss with gliosis. Thalamic nuclei may also be affected. In the basal ganglia, thread-like processes are often extensive, often in the pencil fibers of the striatum. Tau-positive neurons, but not NFT, are common in the striatum and globus pallidus. The internal capsule and thalamic fasciculus often have many thread-like processes. The subthalamic nucleus usually has a normal neuronal population, but neurons may have tau inclusions, and there may be many thread-like lesions in the nucleus. Fibrillary gliosis typical of PSP is not seen in the subthalamic nucleus in CBD.

The substantia nigra usually shows moderate to severe neuronal loss with extraneuronal neuromelanin and gliosis. Many of the remaining neurons contain NFT, which have also been termed "corticobasal bodies" (35) (Fig. 5). The locus ceruleus and raphe nuclei have similar inclusions. In contrast to PSP, where neurons in the pontine base almost always have at least a few NFT, the pontine base is largely free of NFTs in CBD. On the other hand, tau inclusions in glia and thread-like lesions are frequent in the pontine base. The cerebellum has mild Purkinje cell loss and axonal torpedoes. There is also mild neuronal loss in the dentate nucleus, but grumose degeneration is much less common than in PSP.

In CBD the filaments have a paired helical appearance at the electron microscopic level, but the diameter is wider and the periodicity is longer than the paired helical filaments of AD (34). These structures have been referred to as twisted ribbons. Similar to PSP, abnormal insoluble tau in CBD migrates as two prominent bands (68 and 64 kDa) on Western blots (32).

FIGURE 5 CBD: The hallmark lesion in CBD is the astrocytic plaque (asterisk), which is a cluster of irregular tau processes around a central astrocyte (a). The white matter and gray matter in CBD has numerous tau-immunoreactive thread-like processes (b). Cortical neurons have swelling characteristic of ballooning degeneration (c), and the ballooned neurons have intense immunoreactivity with the stress protein alpha-B-crystallin (d). Neurons in the substantia nigra have round inclusions called corticobasal bodies (arrow in e) that are positive for tau (arrow in f). Note also the many thread-like processes in (f).

POSTENCEPHALITIC PARKINSONISM

Parkinsonism following encephalitis lethargica during the influenza pandemic between 1916–1926 is known as postencephalitic parkinsonism (PEP). During the recovery phase of the acute viral encephalitis, parkinsonian rigidity developed with the most characteristic clinical features being oculogyric crises. The PEP brain has NFTs in cortex, basal ganglia, thalamus, hypothalamus, substantia nigra, brainstem tegmentum, and cerebellar dentate nucleus (36). The distribution of the pathology overlaps with PSP, and in recent studies it has not been possible to distinguish the two disorders by histopathological analysis alone (36). Biochemical studies of abnormal insoluble tau in PEP have features similar to AD with three major bands (68, 64, and 60 kDa) on Western blot studies, and electron microscopy shows paired helical filaments similar to those in AD (37).

GUAM PARKINSON-DEMENTIA COMPLEX

A characteristic parkinsonism with dementia (Parkinson dementia complex, PDC) with a number of features that overlap with PSP has been reported in the native Chamorro population of Guam since the 1950s (38). The frequency of PDC has declined in recent years for unknown reasons, and the etiology is unknown. The gross findings in PDC are notable for cortical atrophy affecting frontal and temporal lobes, as well as atrophy of the hippocampus and the tegmentum of the rostral brainstem (39). These areas typically have neuronal loss and gliosis with many NFTs in residual neurons. Extracellular NFTs are also numerous. In the cortex NFTs show a different laminar distribution from AD, with more NFTs in superficial cortical layers in Guam PDC and in lower cortical layers in AD (40). The hippocampus has numerous NFTs. The substantia nigra and locus ceruleus also have marked neuronal loss and many NFTs. The basal nucleus and large neurons in the striatum are also vulnerable to NFTs. Biochemically and morphologically, NFTs in Guam PDC are indistinguishable from those in AD (41).

DEMENTIA PUGILISTICA

An akinetic-rigid syndrome with dysarthria and dementia is sometimes a long-term outcome of repeated closed-head trauma, as seen in professional boxers. The pathology on gross examination, other than lesions that can be attributed to trauma, e.g., subdural membranes and cortical contusions, is nonspecific (42). The substantia nigra may also show pigment loss. Microscopically, there are NFTs similar to those in AD in brainstem monoaminergic nuclei, cortex, and hippocampus. At the electron micro-

scopic level, they are composed of paired helical filaments and biochemically composed 68, 64, and 60 kDa forms (43).

FAMILIAL PARKINSONISM

While most parkinsonian disorders are sporadic, rare familial forms have been described and mutations have been found or genetic linkage analyses have suggested a strong genetic factor in their etiology (44). Perhaps the most common familial PD is autosomal recessive juvenile Parkinson's disease (ARJP). The clinical features are somewhat atypical in that dystonia is common in ARJP (45). The pathology of ARJP is based upon only a few autopsy reports. Initial studies emphasized severe neuronal loss in the substantia nigra with no LBs, but a more recent report of an individual who died prematurely in an automobile accident had LBs in the substantia nigra and other vulnerable regions (46). Even in sporadic PD there is an inverse relationship between the disease duration and the number of LBs in the substantia nigra. When the disease is very severe, there are very few residual neurons. Since LBs are intraneuronal inclusions that are phagocytosed after the neuron dies, it is not surprising that there are few LBs in cases of long duration.

Less common than ARJP are autosomal dominant forms of PD. The best characterized is the Contursi kindred, a familial PD due to a mutation in the α-synuclein gene (47). The pathology of the Contursi kindred is typical LB Parkinson's disease; however, given the young age of onset, by the time the individual dies, LB pathology is typically widespread in the brain. Lewy neurites are also prominent in many cortical areas.

Late-onset familial PD, such as Family C, has clinical characteristics and pathology that is virtually indistinguishable from sporadic PD (48). Some young-onset autosomal dominant PD kindred, such as the Iowa kindred, have atypical clinical presentations and include family members with dementia and psychosis. The pathology in at least some of these cases is associated with severe LB-related pathology in the cortex, hippocampus, and amygdala, in addition to the substantia nigra and other brainstem nuclei and in some cases glial inclusions similar to those in MSA are present (Fig. 6) (49).
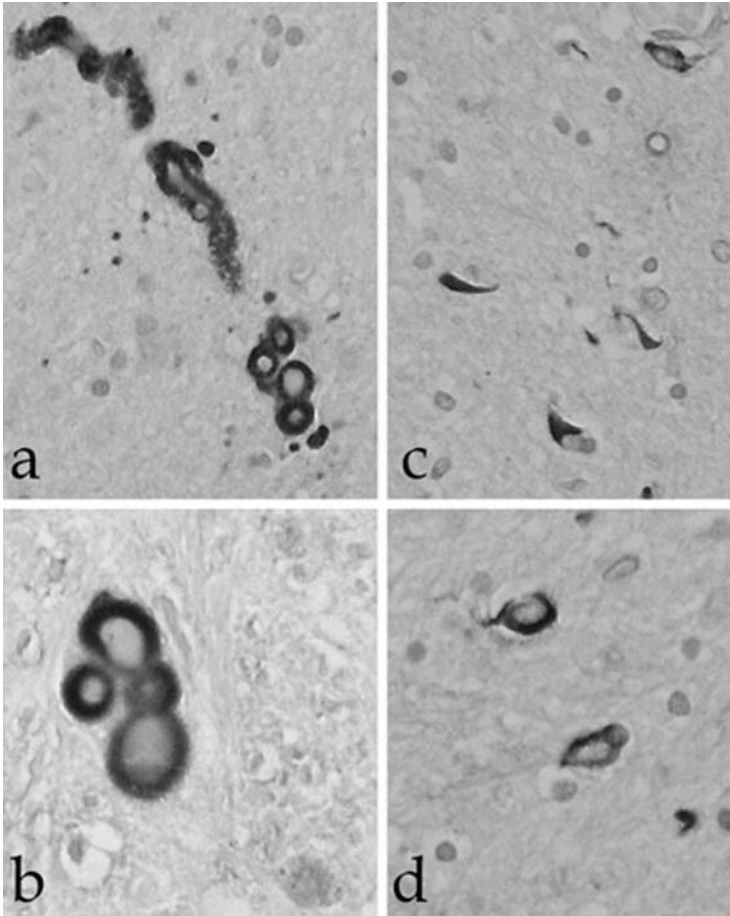
FIGURE 6 Familial PD: Many Lewy bodies are detected in early-onset familial cases, and some of the inclusions have unusual morphologies (a, b). Like MSA, synuclein-immunoreactive glial inclusions are also detected in some cases of familial early-onset PD.

ACKNOWLEDGMENTS

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