

Parkinson's Disease and Parkinsonism: Neuropathology

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Parkinsonism, the clinical term for a disorder with prominent bradykinesia and variable associated extrapyramidal signs and symptoms, is accompanied by degeneration of the nigrostriatal dopaminergic system, with neuronal loss and reactive gliosis in the substantia nigra found at autopsy. Parkinsonism is pathologically heterogeneous, with the most common pathologic substrates related to abnormalities in the presynaptic protein α -synuclein or the microtubule binding protein tau. In idiopathic Parkinson's disease (PD), α -synuclein accumulates in neuronal perikarya (Lewy bodies) and neuronal processes (Lewy neurites). The disease process is multifocal and involves select central nervous system neurons and peripheral autonomic nervous system neurons. The particular set of neurons affected determines nonmotor clinical presentations. Multiple system atrophy (MSA) is the other major α -synucleinopathy. It is also associated with autonomic dysfunction and in some cases with cerebellar signs. The hallmark histopathologic feature of MSA is accumulation of α -synuclein within glial cytoplasmic inclusions (GCI). The most common of the Parkinsonian tauopathies is progressive supranuclear palsy (PSP), which is clinically associated with severe postural instability leading to early falls. The tau pathology of PSP also affects both neurons and glia. Given the population frequency of PD, α -synuclein pathology similar to that in PD, but not accompanied by neuronal loss, is relatively common (10% of people over 65 years of age) in neurologically normal individuals, leading to proposed staging schemes for PD progression. Although MSA-like and PSP-like pathology can be detected in neurologically normal individuals, such cases are too infrequent to permit assessment of patterns of disease progression.

Parkinson's disease (PD) is a progressive neurological disorder defined by a characteristic clinical syndrome by bradykinesia, tremor, rigidity, and postural instability. There are a large number of different disorders that can have some or all of these clinical features, and the clinical syndrome is referred to as "parkinsonism." Disorders in which parkinsonism is a

prominent part are referred to as "parkinsonian disorders." PD is but one of a host of parkinsonian disorders (Table 1). Some parkinsonian disorders are chronic and progressive and caused by an unknown degenerative disease process, whereas others may have clear genetic cause, such as cases driven by autosomal dominant mutations in the gene for α -synuclein. Others

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Table 1. Parkinsonian disorders

Classification	Examples
Degenerative parkinsonism	
α-Synuclein	Parkinson's disease, multiple system atrophy
Tau	Progressive supranuclear palsy, corticobasal degeneration, Guam parkinson dementia complex, chronic traumatic encephalopathy
TDP-43	Frontotemporal lobar degeneration (FTLD-TDP)
Nondegenerative parkinsonism	
Vascular	Vascular parkinsonism
Toxic	MPTP, manganese poisoning
Drug-induced	Antipsychotic medications
Infectious	Influenza virus (postencephalitic parkinsonism)

can be transient and caused by effects of toxins, metabolic disturbances, or drugs. The latter may have no telltale sign with standard pathological methods and can be considered “functional” rather than “structural” disorders. Some toxins that cause parkinsonism (e.g., MPTP induced parkinsonism) produce lasting brain damage that leaves structural changes.

It is important to emphasize that it is not possible to diagnose parkinsonism with neuropathologic methods; it is only possible to describe pathologic findings—histologic, neurochemical, and molecular—that are frequently associated with parkinsonism.

Degenerative parkinsonian disorders can be inherited or sporadic, but are all characterized by neuronal loss in selective populations of vulnerable neurons. The common denominator of all degenerative parkinsonian disorders is loss of dopaminergic neurons of the substantia nigra that project to the putamen (i.e., dopaminergic nigrostriatal pathway) (Figs. 1 and 2).

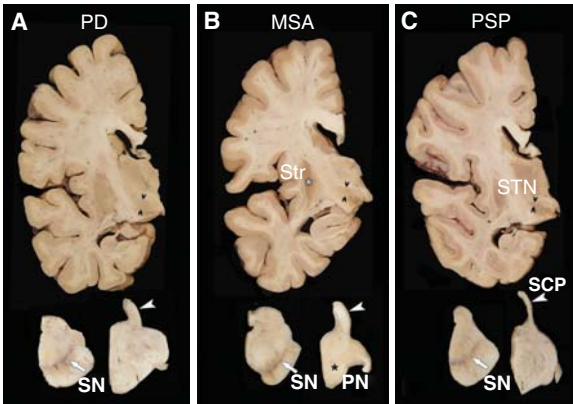


Figure 1. Macroscopic appearance of the brain in PD (A), MSA (B), and PSP (C). There are distinguishing macroscopic features in these three major degenerative parkinsonian disorders, which is also the basis of neuroimaging biomarkers in the living patient. Transverse sections of the midbrain (lower left) and pons (lower right) shows pigment loss in the substantia nigra (white arrows) in all three disorders, which correlates with parkinsonism. In MSA there is atrophy of the pontine base (black asterisk in B), whereas the pontine base is unremarkable in PD and PSP. In PSP the superior cerebellar peduncle (compare structures marked with white arrowheads in A–C) has marked atrophy in C, whereas it has normal thickness in PD and MSA. Sections of the cerebrum at the level of the subthalamic nucleus show atrophy in PSP (C) (double black arrowheads mark the widest diameter of the nucleus), whereas the STN is normal in PD (A) and MSA (B). In MSA there is atrophy and dark discoloration of the posterior putamen (white asterisk in B), but no atrophy or discoloration is noted in PD or PSP. Abbreviations: SN, substantia nigra; Str, striatum; PN, pontine nuclei; SCP, superior cerebellar peduncle; STN, subthalamic nucleus.

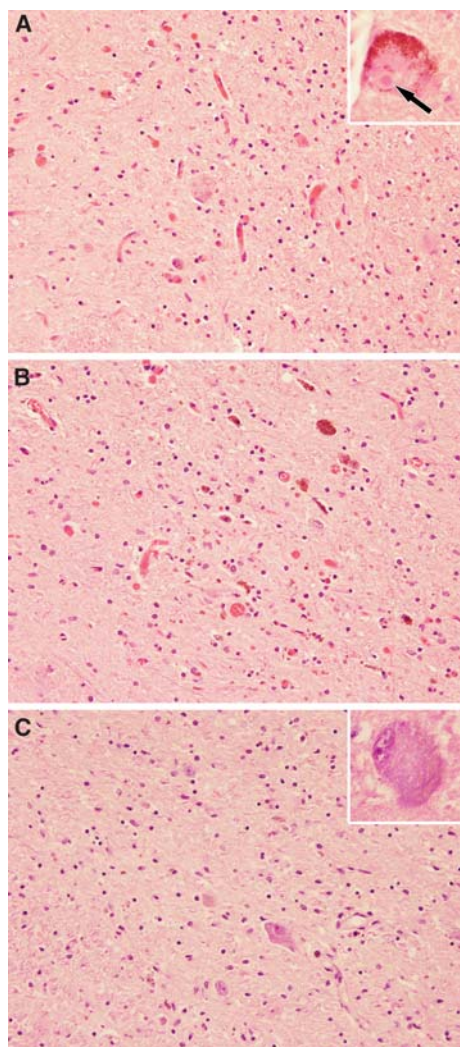


Figure 2. Substantia nigra in PD (A), MSA (B), and PSP (C). All three major degenerative parkinsonian disorders have neuronal loss, extraneuronal neuromelanin pigment, and gliosis in the substantia nigra, especially the ventrolateral tier (shown here). There are no distinctive histologic features in MSA, but in PD there are typical hyaline cytoplasmic inclusions—Lewy bodies (*inset* in A), whereas PSP is characterized by basophilic globose shaped neurofibrillary tangles (*inset* in C).

Degenerative diseases can be classified a number of ways, but increasingly, pathologists classify them based on molecular mechanisms. Many of the most common degenerative diseases have onset in mid-to-late adulthood and

have pathologic accumulations of normal cellular proteins within vulnerable neuronal populations. Most degenerative parkinsonian disorders fall into one of two molecular classes—tauopathies and α -synucleinopathies—based on pathologic accumulation of the microtubule associated protein tau or the presynaptic protein α -synuclein within vulnerable neurons and often within glial cells, as well.

PD is a degenerative parkinsonian disorder characterized by neuronal inclusions composed of α -synuclein. The inclusions are located in neuronal perikarya and referred to as Lewy bodies (Fig. 2A inset and Fig. 3A,B). Similar inclusions within neuronal cell processes are referred to as Lewy neurites (Fig. 3C). The combination of Lewy bodies and Lewy neurites is sometimes referred to as Lewy-related pathology (Dickson et al. 2009), because it is increasingly clear that abnormal α -synuclein accumulation in neuronal perikarya may be the tip of the iceberg, with evidence of accumulation not only in neuronal cell processes (Irizarry et al. 1998), but also with the synaptic compartment (Muntane et al. 2008; Schulz-Schaeffer 2010).

The other major degenerative parkinsonian disorder characterized by inclusions composed of α -synuclein is multiple system atrophy (MSA), a parkinsonian disorder that affects not only the nigrostriatal dopaminergic pathway, but also the cerebellar afferent pathways (pontocerebellar and olivocerebellar fibers). Neuronal inclusions in MSA (Fig. 4B,C), however, are a minor component of the pathology. In contrast, α -synuclein inclusions within the cytoplasm of oligodendroglial cells, so-called glial cytoplasmic inclusions (Lantos 1998), are the major finding (Fig. 4A). Interestingly, neurons in MSA may also have α -synuclein inclusions within their nuclei (Fig. 4D) (Lin et al. 2004), a feature not seen in affected neurons in PD.

The most common of the degenerative parkinsonian disorders associated with neuronal inclusions composed of tau protein is progressive supranuclear palsy (PSP), in which there are also tau inclusions within glial cells (both astrocytes and oligodendrocytes) (Fig. 5) (Dickson 2007). PSP is sometimes referred to as a “parkinsonism-plus” disorder in that the clinical

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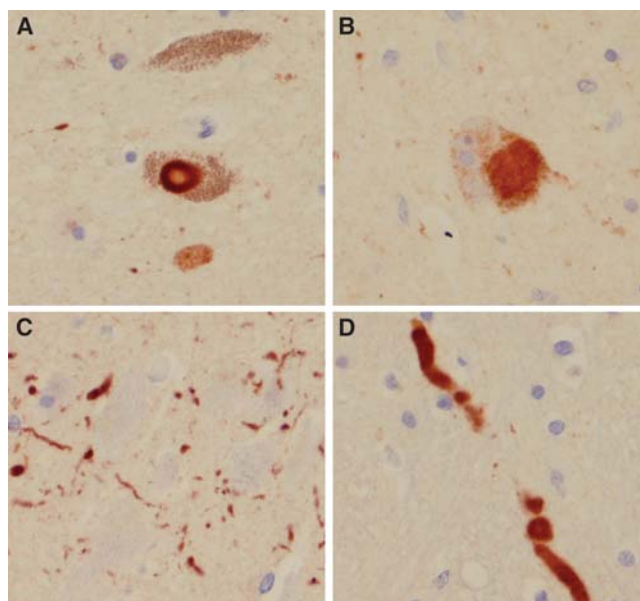


Figure 3. Microscopic findings in PD with α -synuclein immunohistochemistry. A typical brainstem type Lewy body (A) and a pale staining "cortical type" Lewy body (B), Lewy neurites in CA2 sector of hippocampus (C), and intraneuritic Lewy bodies in medulla (D).

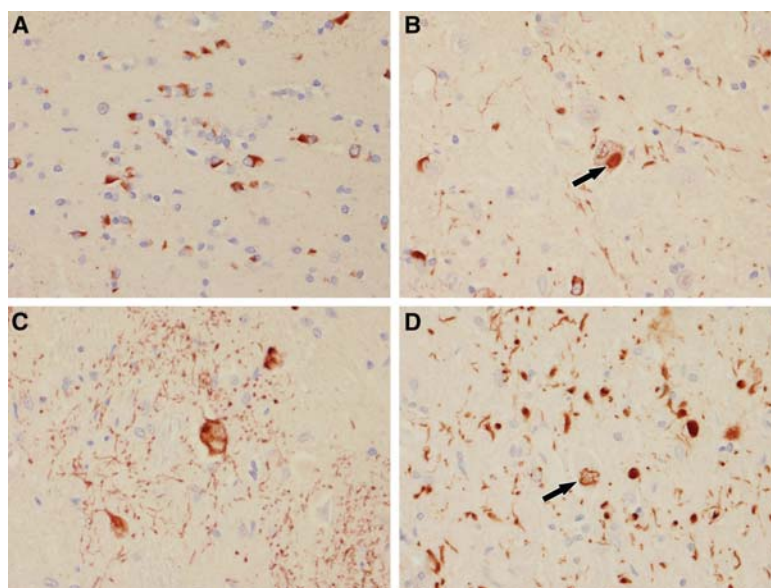


Figure 4. Microscopic findings in MSA with α -synuclein immunohistochemistry. Glial cytoplasmic inclusions in pencil fibers of the putamen (A), neuronal cytoplasmic inclusion in pontine nuclei (arrow in B), neuronal cytoplasmic inclusions and dystrophic neurites in the inferior olivary nucleus (C), and intranuclear inclusions (arrow) and dystrophic neurites in the pontine nucleus (D).

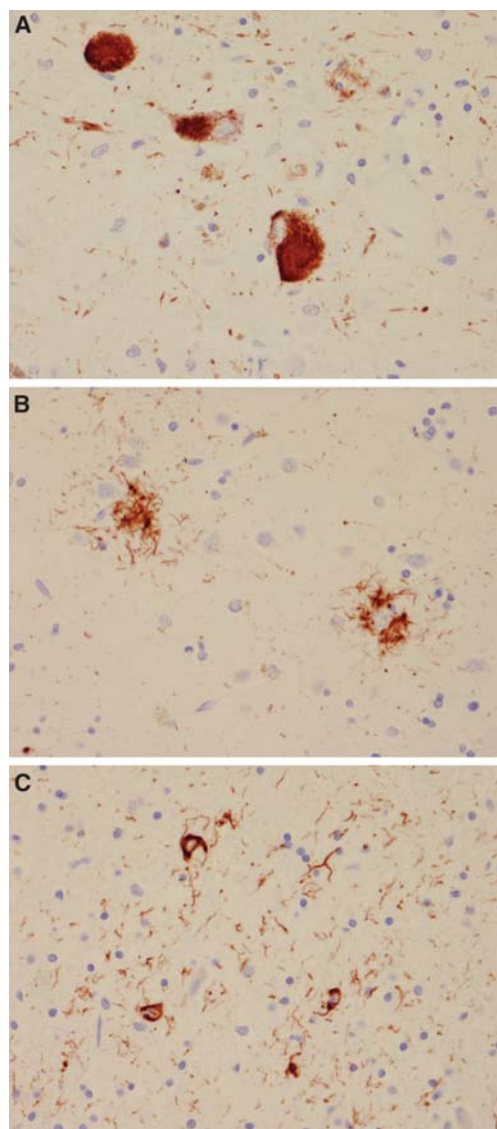


Figure 5. Microscopic examination of PSP with tau immunohistochemistry. Globus neurofibrillary tangles (A), tufted astrocytes (B), and coiled bodies (C). Note also tau positive neurites in A and C.

features consistently include other neurologic features not clearly related to parkinsonism, such as eye movement disorder and dementia (Steele et al. 1964). This corresponds to involvement of brain regions beyond the dopaminergic neurons of the nigrostriatal pathway. MSA is also a “parkinsonism-plus” disorder because

patients invariably have evidence of autonomic dysfunction and often signs of cerebellar dysfunction, such as nystagmus and ataxia.

The concept of as a “parkinsonism-plus” disorder has become increasingly muddled as it clear that most patients with PD also have nonparkinsonian clinical features, such as autonomic dysfunction, sleep disorders, and eventually dementia (Langston 2006). Indeed, Lewy bodies and Lewy neurites are not confined to the nigrostriatal system in PD, but can be widespread in peripheral and central autonomic neurons, even the cerebral cortex (Braak and Del Tredici 2009).

The focus of this article will be on the pathology of the most common of the degenerative parkinsonian disorders—PD, MSA, and PSP. The discussion will compare and contrast their clinical, macroscopic, and microscopic features. The rationale for limiting the discussion to these three disorders is that in autopsy series of parkinsonism, these are the most common diagnoses and clinically the most important differential diagnosis. The most common nondegenerative cause of parkinsonism found in autopsy series is cerebrovascular disease, which produces a disorder referred to as “vascular parkinsonism” (Zijlmans et al. 2004). Given heterogeneity of cerebrovascular pathology (e.g., infarcts, hemorrhages, and white matter pathology) and the neuroanatomical distribution of these lesions (e.g., basal ganglia, thalamus, and brainstem), the clinical and pathological criteria of vascular parkinsonism are less well established. The last section provides a brief overview of pathologic features other degenerative parkinsonian disorders.

CLINICAL COMPARISON OF PD, MSA, AND PSP

Characteristic Clinical Features of PD

PD can be diagnosed with considerable accuracy, particularly by neurologists specializing in diagnosis and management of movement disorders (Hughes et al. 2002), when robust clinical criteria are used such as those of the Queen Square Parkinson Disease Brain Bank, which

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have inclusion criteria (bradykinesia and at least one of rigidity, tremor, or postural instability) and exclusion criteria (absence of strokes, head injury, encephalitis, neuroleptic treatment, supranuclear gaze palsy, cerebellar signs, early severe autonomic dysfunction, early dementia pyramidal tract, exposure to toxins signs) as well as presence of supportive features (chronic progressive disease course, unilateral onset and asymmetry of signs during disease course, excellent and prolonged response to levodopa, late levodopa-induced dyskinesia). Asymmetry is an important supportive feature in that the other major degenerative parkinsonian disorders MSA and PSP are usually symmetrical. Response to dopamine replacement therapy (e.g., levodopa or dopamine agonists) is typical of PD, whereas MSA and PSP have limited response to such therapy. The exclusion criteria also include absence of family history of movement disorder, but this is criterion is often ignored today given increasing evidence of genetic determinants of PD (Farrer 2006).

Some of the exclusion criteria are meant to rule out PSP (e.g., supranuclear gaze palsy) and MSA (e.g., cerebellar signs and early severe autonomic dysfunction) (Table 2), but it is increasingly recognized that autonomic dysfunction is common in PD and that it may also be an early feature of the disease, given recent evidence that peripheral nerves and ganglia of the autonomic nervous system are affected early in PD and may actually be affected prior to significant brain involvement (Langston 2006; Lang 2007). It is of interest that epidemiologic studies indicate that autonomic symptoms may precede clinical PD by more than a decade (Abbott et al. 2001). Another clinical syndrome that may be a harbinger of PD is rapid eye movement behavior disorder (RBD), a condition that ap-

pears a number of years before PD (Schenck et al. 1996). The RBD syndrome appears to have its anatomic origins within lower brain-stem nuclei (Kayama and Koyama 2003) that are consistently affected in PD. Olfactory dysfunction is common in PD (Hawkes et al. 1997), and it may also precede motor symptoms (Bendse et al. 2001). The later stages of PD have involvement of the cerebral cortex and at this state of the disease, PD is characterized by cognitive dysfunction or frank dementia, referred to as PD dementia. PD dementia is distinguished from dementia with Lewy bodies (McKeith et al. 2004), in which dementia is an early and prominent clinical feature.

Characteristic Clinical Features of MSA

MSA is a nonheritable neurodegenerative disorder characterized by parkinsonism, cerebellar ataxia and idiopathic orthostatic hypotension (also known as Shy-Drager syndrome), a syndrome complex first recognized by Oppenheimer, who noted overlap in the pathology of sporadic olivopontocerebellar atrophy and striatonigral degeneration (Oppenheimer 1976). Depending on the predominant signs and symptoms, MSA is subdivided into MSA-C, for those with predominant degeneration in cerebellar circuitry and ataxia, and MSA-P for those with predominant degeneration in the basal ganglia with parkinsonism (Gilman et al. 1999). Autonomic dysfunction is required for the clinical diagnosis of MSA, but as noted above can also be seen in PD. It is rare in PSP.

Characteristic Clinical Features of PSP

One of the earliest clinical features of PSP is unexplained falls. Eventually, most patients with PSP develop postural instability, vertical gaze

Table 2. Clinical differential diagnosis

	PD	MSA	PSP
Asymmetrical motor signs	Almost always	Sometimes	Sometimes
Levodopa response	Almost always	Sometimes	Sometimes
Autonomic dysfunction	Sometimes	Always	Almost never
Dementia	Almost always, late in the disease	Almost never	Almost always, in some cases early



paresis, nuchal and axial rigidity, and dysarthria. Despite many differences in clinical presentation, it is not uncommon for an individual to carry a diagnosis of PD for years before a correct diagnosis of PSP is made (Rajput et al. 1991; Josephs and Dickson 2003). Recently, it has been suggested that a subset of cases of pathologically confirmed PSP have parkinsonism with many similarities to PD, including asymmetry, tremor and partial response to levodopa, PSP-P (Williams et al. 2005). Many patients with PSP have cognitive problems or dementia, but this does not help to differentiate PSP from PD, because late in the disease process PD patients also frequently develop dementia (Hely et al. 2008) and even early in the disease, PD patients may have mild cognitive deficits compared to healthy individuals. On the other hand, most MSA patients have better preservation of cognition.

NEUROPATHOLOGY OF PARKINSONISM

Macroscopic Pathology—PD, MSA, PSP

PD is often unremarkable, with mild frontal atrophy in some cases. There is no significant atrophy of brainstem, and this can be useful in the differential diagnosis of PSP and MSA, in which there is midbrain atrophy in PSP and pontine atrophy in MSA. Sections of the brainstem usually reveal loss of the normally dark black pigment in the substantia nigra (Fig. 2) and locus ceruleus, but pigment loss in the substantia nigra is also characteristic of PSP and MSA. The loss of pigmentation correlates with neuronal loss of dopaminergic neurons in the substantia nigra and noradrenergic neurons in the locus ceruleus. Pigment loss in the locus ceruleus is consistent in PD, but less predictable in PSP and MSA.

MSA-P has atrophy and brownish discoloration of the posterolateral putamen (Fig. 1), the brown color correlating with increased iron pigment. In cases with significant cerebellar signs, there is also atrophy of the pontine base and atrophy and gray discoloration of the cerebellar white matter. More subtle atrophy is noted in the medulla (e.g., inferior olive) and the cerebellar cortex.

PSP has mild frontal cortical atrophy and often-marked atrophy of the midbrain. The latter is uncommon in PD and MSA. The cerebellar dentate nucleus usually has atrophy and discoloration of the white matter in the dentate hilus, with similar atrophy and discoloration in the cerebellar outflow pathway. This produces marked atrophy of the superior cerebellar peduncle (Fig. 1). The basal ganglia and thalamus are usually macroscopically unremarkable, but the subthalamic nucleus is almost always smaller than normal and often discolored (Fig. 1). The subthalamic nucleus and the superior cerebellar peduncle are not affected in PD or MSA.

MICROSCOPIC PATHOLOGY

Lewy Bodies and Lewy-Related Pathology in PD

Classical Lewy bodies have a hyaline appearance on H&E (Fig. 2A inset), whereas α -synuclein immunoreactive inclusions in less vulnerable neuronal populations, such as the amygdala and cortex, are pale staining and poorly circumscribed. These lesions are referred to as “cortical Lewy bodies” (Ikeda et al. 1978). A related pale staining neuronal cytoplasmic inclusion found in pigmented brainstem neurons of the substantia nigra and locus ceruleus is the “pale body” (Pappolla et al. 1988; Dale et al. 1992). Evidence suggests that cortical Lewy bodies and pale bodies may be early cytologic alterations that precede the classical Lewy body, so-called pre-Lewy bodies. In some cases with severe pathology, hyaline type inclusions consistent with classical Lewy bodies can be detected in the amygdala and cortex, particularly the limbic cortex. Although most of the α -synuclein immunoreactive cytopathology in PD is within neurons, α -synuclein immunoreactive glia, particularly oligodendroglia, can be detected in small numbers in the midbrain and basal ganglia (Wakabayashi and Takahashi 1996; Wakabayashi et al. 2000).

At the ultrastructural level, Lewy bodies are composed of dense granular material and straight filaments that are approximately 10–15nm in diameter (Forno 1969; Tiller-Borich

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and Forno 1988; Galloway et al. 1992). Similar filaments can be created in the test tube with recombinant α -synuclein (Conway et al. 2000; Crowther et al. 2000). The presence of α -synuclein in cytoplasmic inclusions represents aberrant cytologic localization, because α -synuclein is normally a component of presynaptic terminals. The factors that give rise to the abnormal conformation remain to be determined, but several posttranslational modifications, including phosphorylation, truncation, and oxidative damage are implicated (reviewed by Dickson 2001). The composition of the dense granular material in Lewy bodies is unknown, but perhaps related to other components that have been shown to be present in Lewy bodies. Antibodies to neurofilament (Galvin et al. 1997), ubiquitin (Kuzuhara et al. 1988), and the ubiquitin binding protein p62 (Kuusisto et al. 2003) are among the most consistently detected proteins in Lewy bodies. A subset of Lewy bodies shows immunoreactivity with antibodies to tau protein (Ishizawa et al. 2003), but this is a small subset of Lewy bodies and almost always in neuronal populations that are inherently vulnerable to tau pathology. It is rare to find tau immunoreactivity in cortical type Lewy bodies in PD. Many other antibodies that inconsistently label Lewy bodies have been reported (Pollanen et al. 1993).

Glial Cytoplasmic Inclusions in MSA

Lantos and co-workers first described glial (oligodendroglial) cytoplasmic inclusions in MSA (6). Glial cytoplasmic inclusions can be detected with silver stains, in particular, the Gallyas silver stain, but are best seen with antibodies to α -synuclein (Fig. 4A) and ubiquitin, in which they appear as flame- or sickle-shaped inclusions in oligodendrocytes. At the ultrastructural level, glial cytoplasmic inclusions are nonmembrane-bound cytoplasmic inclusions composed of 10 to 20nm diameter coated filament similar to the filaments in Lewy bodies (Lin et al. 2004).

Although most α -synuclein inclusions in MSA are in oligodendroglial cells, certain neuronal populations are vulnerable to neuronal

cytoplasmic and intranuclear inclusions, particularly those in the pontine base (Fig. 4A), inferior olive (Fig. 4C), and putamen. A few of the neuronal inclusions in MSA resemble Lewy bodies, but their anatomical distribution is distinct from neuronal populations vulnerable to Lewy bodies. Intranuclear α -synuclein-immunoreactive inclusions (Fig. 4D) (Lin et al. 2004) are not found in PD.

Neuronal and Glial Tau Pathology in PSP

PSP is a degenerative tauopathy characterized by accumulation of filamentous tau inclusions within neurons. Tau is a microtubule associated protein that is biochemically composed of six major isoforms related to alternative mRNA splicing, including three isoforms with four \sim 32-amino acid conserved repeats (4R-tau) in the microtubule binding domain and three isoforms with three repeats (3R tau). In PSP, 4R tau preferentially accumulates, whereas in Alzheimer's disease tau inclusions are composed on a nearly equal mixture of 3R and 4R tau. Monoclonal antibodies specific to 3R and 4R tau now permit assessment of the type of tau that accumulates within neuronal lesions with routine immunohistochemistry (de Silva et al. 2003).

In addition to neurofibrillary tangles (Fig. 5A), tau pathology of PSP is characterized by inclusions in astrocytes (so-called "tufted astrocytes") (Fig. 5B) and in oligodendroglia (so-called "coiled bodies") (Fig. 5C). The latter glial lesions are distinct from the glial cytoplasmic inclusions of MSA and the sparse glial lesions detected in PD, not only based on their immunoreactivity with tau, but also on their morphology. Tau also accumulates in cell processes (both neuronal and glial), referred to as tau-positive "threads."

Distribution of Pathology

The hallmark of any neurodegenerative disease is selective neuronal loss (Table 3). Accompanying neuronal loss in all neurodegenerative disorders are reactive changes in astrocytes and microglia. Microglia express markers of activation,

Table 3. Pathologic comparison of PD, MSA, and PSP

Region	PD	MSA	PSP
Amygdala	Consistent/severe	Spared	Spared
Hippocampus	Variable/moderate	Spared	Spared
Temporal cortex	Variable/moderate	Spared	Spared
Cingulate cortex	Variable/moderate	Uncommon/mild	Spared
Superior frontal gyrus	Uncommon/mild	Spared	Variable/moderate
Motor cortex	Spared	Variable/moderate	Consistent/severe
Caudate/putamen	Uncommon/mild	Consistent/severe	Consistent/severe
Globus pallidus	Spared	Variable/moderate	Consistent/severe
Basal nucleus of Meynert	Consistent/severe	Uncommon/mild	Consistent/severe
Hypothalamus	Consistent/severe	Uncommon/mild	Consistent/severe
Thalamus	Spared	Uncommon/mild	Consistent/severe
Subthalamic nucleus	Spared	Spared	Consistent/severe
Red nucleus	Spared	Spared	Variable/moderate
Substantia nigra	Consistent/severe	Consistent/severe	Consistent/severe
Oculomotor complex	Variable/moderate	Spared	Consistent/severe
Midbrain tectum	Spared	Spared	Consistent/severe
Locus ceruleus	Consistent/severe	Uncommon/mild	Consistent/severe
Pontine tegmentum (including raphe and pedunculopontine nuclei)	Variable/moderate	Uncommon/mild	Consistent/severe
Pontine nuclei (including pontocerebellar fibers)	Spared	Consistent/severe	Variable/moderate
Medullary tegmentum (including dorsal motor nucleus of vagus)	Consistent/severe	Consistent/severe	Consistent/severe
Inferior olive (including olivocerebellar fibers)	Spared	Consistent/severe	Variable/moderate
Dentate nucleus	Spared	Spared	Consistent/severe
Cerebellar white matter	Spared	Consistent/severe	Uncommon/mild

such as the class II major histocompatibility antigen HLA-DR (McGeer et al. 1988), and astrocytes become hypertrophic and accumulate the intermediate filament protein, glial fibrillary acidic protein. Dying neurons undergo phagocytosis by microglia, a term referred to as neurophagia. In the substantia nigra and locus ceruleus, evidence of neuronophagia is neuromelanin pigment in the cytoplasm of microglia. In cases with very long disease duration, microglia migrate to blood vessels and exit the brain along with the neuromelanin pigment. Neuronal loss in the substantia nigra is most marked in the ventrolateral tier of neurons of the pars compacta (A9) in all parkinsonian disorders. In contrast, the dorsal and medial neuronal cell groups are less vulnerable. Loss of medial neuronal cell groups (e.g., ventral tegmental region or A10) may be increased in parkinsonian disorders with dementia (Rinne et al. 1989).

Braak PD Staging Scheme

It has been known for many years that Lewy bodies in PD extend well beyond the substantia nigra (Jellinger 1991). Based on the distribution of α -synuclein pathology, Braak and co-workers have proposed a staging scheme for PD (Braak et al. 2004). In this scheme, neuronal pathology occurs early in the dorsal motor nucleus of the vagus in the medulla and the anterior olfactory nucleus in the olfactory bulb. As the disease progresses, locus ceruleus neurons in the pons and then dopaminergic neurons in the substantia nigra are affected. In later stages, pathology extends to the basal forebrain, amygdala and the medial temporal lobe structures, with convexity cortical areas affected in the last stages. Although the staging scheme is attractive, it should be remembered that this scheme is not based on distribution of neuronal loss, but



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on distribution of abnormal α -synuclein deposits and how it relates to progression of neuronal loss has not been rigorously studied. Thus, the proposed staging should be interpreted cautiously. The scheme was originally based on evaluation of brains of individuals that were not necessarily well characterized in life, and cases were chosen for further study if they had pathology in the medulla (Del Tredici et al. 2002), thus, biasing the results in favor of “early” pathology in the medulla. In more recent studies of prospectively studied individuals who have come to autopsy, the scheme proposed by Braak and co-workers does not always hold true. Some elderly individuals have Lewy bodies confined to the olfactory bulb (Fujishiro et al. 2008a; Beach et al. 2009) or the amygdala, the latter particularly true if associated with concurrent Alzheimer type pathology (Uchikado et al. 2006). Moreover, some neurologically normal individuals have sparse, but widespread Lewy body pathology, even involving the cortex (Parkkinen et al. 2005; Frigerio et al. 2011), which would seem to violate the theory of progression from brainstem and perhaps fit better with a multicentric disease process from the onset. Clearly, the observed distribution of Lewy bodies is dependent on case selection (Parkkinen et al. 2001).

Although the staging scheme of Braak and co-workers should be considered tentative, it nevertheless, has prompted considerable debate in the field and reawakened recognition of early nonmotor clinical features of PD (Jain 2011). Subsequent iterations of the Braak scheme proposed that autonomic neurons in peripheral nervous system may be affected before involvement of the central nervous system (Braak and Del Tredici 2009) and this has prompted recognition that PD is a multiorgan disease process, not merely a disorder of central nervous system (Beach et al. 2010). Moreover, it has fed the debate on cell-to-cell transmission of unknown putative disease factors (prion-like) (Hawkes et al. 2009), especially given the fact that fetal mesencephalic intraatrial transplants to treat PD have been shown to develop Lewy body pathology (Kordower et al. 2008), possibly by cell-to-cell transmission (Kordower et al. 2011).

Jellinger Staging Scheme for MSA

It has been more challenging to stage pathology in MSA and PSP because of the rarity of these disorders and because of their inherent variability. Nevertheless, Jellinger has proposed a staging scheme for MSA that scores severity of striatonigral degeneration (SND) and olivopontocerebellar atrophy (OPCA), each on a three-point scale. The final classification is indicated by an OPCA + SND score (e.g., OPCA 1 + SND 3 for a typical MSA-P case and OPCA 3 + SND 1 for a typical MSA-C case). Halliday and co-workers (2011) proposed a similar scheme and graphically illustrated the two major MSA types, as well as the overlap in OPCA and SND system degenerations. Ozawa and colleagues used a semiquantitative scoring scheme for lesion density and found differences in the proportion of MSA types in Japanese compared to European autopsy cohorts, with far more OPCA in Japanese (Ozawa et al. 2004, 2010). Detection of MSA in neurologically normal individuals (“incidental MSA”) is extremely uncommon (Fujishiro et al. 2008b), and large numbers of such cases would be needed to determine the earliest sites of involvement to develop a staging scheme for MSA analogous to the Braak staging scheme for PD.

Distribution of Pathology in PSP

The distribution neuronal loss and neurofibrillary degeneration in PSP was beautifully documented in the original report by Steele, Richardson, and Olszewski based on classic silver staining methods (Steele et al. 1964). Modern neuropathologic methods with tau immunohistochemistry have extended these observations, by recognizing glial involvement, as well as greater cortical pathology than noted in the original report, particularly affecting motor and premotor cortices of the frontal lobe (Hauw et al. 1990). Nevertheless, the cardinal nuclei affected in PSP remain those originally described and include the globus pallidus, subthalamic nucleus, substantia nigra, midbrain tectum, periaqueductal gray, locus ceruleus, and the cerebellar dentate nucleus. Other regions that are consistently affected include corpus



striatum, ventrolateral thalamus, red nucleus, pontine and medullary tegmentum, pontine base, and inferior olivary nucleus. Spinal cord involvement is also common, where neuronal inclusions can be found in intermediolateral cell columns. Heterogeneity in the distribution of tau pathology in PSP is increasingly recognized (Williams et al. 2005; Dickson et al. 2010), but a staging scheme remains to be defined. The presence of PSP-like pathology in neurologically normal individuals (“incidental PSP”) is uncommon (Evidente et al. 2011). As in MSA, the paucity of such cases precludes development of staging scheme for PSP.

OTHER DEGENERATIVE PARKINSONIAN DISORDERS

Other Parkinsonian Tauopathies

Corticobasal Degeneration

Corticobasal degeneration (CBD), which is also known as cortical basal ganglionic degeneration, is a parkinsonism-plus disorder with characteristic focal cortical signs in addition to atypical levodopa-nonresponsive parkinsonism (Litvan et al. 1997; Boeve et al. 1999). Patients with CBD may present with progressive asymmetrical rigidity and apraxia (i.e., the corticobasal syndrome), but other clinical syndromes are also reported such as progressive aphasia and progressive frontal lobe dementia (Litvan 1999). Parkinsonism is characterized by bradykinesia, rigidity, and dystonia, but most patients do not have tremor.

The pathologic correlate of focal cortical findings on clinical evaluations is focal cortical atrophy, which is uncommon in PD, MSA, and PD. Cortical atrophy in CBD is often most marked in the superior frontal gyrus, and the motor cortex may be severely affected. The mid-brain does not have 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 (Dickson 1999).

Microscopically, the affected cortical areas have neuronal loss, spongiosis, and gliosis with swollen achromatic or ballooned neurons. Cor-

tical neurons in affected areas have pleomorphic tau-immunoreactive inclusions, and there are invariably numerous tau positive threads in both gray and white matter of affected cortices, as well as in the basal ganglia (Dickson et al. 2002). The most characteristic lesion in CBD is an annular cluster of short, stubby processes with fuzzy outlines that represent tau accumulation in distal processes of astrocytes, a lesion referred to as an “astrocytic plaque” (Feany and Dickson 1995). Astrocytic plaques differ from the tufted astrocytes seen in PSP, and the two lesions do not coexist in the same brain (Komori 1999).

The globus pallidus and putamen show mild neuronal loss with gliosis. Thalamic nuclei may also be affected. The substantia nigra usually shows moderate to severe neuronal loss with extraneuronal neuromelanin, gliosis and tau immunoreactive neuronal lesions. The lower brainstem is less affected than in PSP (Dickson 1999, 2004).

Chronic Traumatic Encephalopathy

Individuals that suffer repeated closed head trauma may develop parkinsonism as well as dementia, a disorder currently referred to as chronic traumatic encephalopathy (CTE) (McKee et al. 2009). In the past, this syndrome was referred to as dementia pugilistica or “punch drunk” syndrome because it was often associated with dementia and parkinsonism in professional boxers. There may be evidence of increasing frequency of the syndrome in other contact sports. In addition to other signs of chronic head trauma, such as small contusions or chronic subdural membrane, patients with CTE also had tau pathology that patchy and predominant in gray matter at the depths of cortical sulci and in superficial cerebral white matter. In these areas, tau accumulates in both neurons and astrocytes. The tau protein that accumulates is biochemically similar to that found in Alzheimer’s disease.

Guam Parkinson-Dementia Complex

A characteristic Parkinsonism with dementia (Parkinson dementia complex [PDC]) with a number of features that overlap with PSP (Steele



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et al. 2002; Steele 2005) is common in the native Chamorro population of Guam and in the Kii peninsula of Japan (Kuzuhara and Kokubo 2005). The gross findings in PDC are notable for cortical atrophy affecting especially the medial temporal lobe, as well as atrophy of the hippocampus and the tegmentum of the rostral brainstem, which overlaps with atrophy seen in Alzheimer's disease. These areas typically have neuronal loss and gliosis with many neurofibrillary tangles in residual neurons and extracellular neurofibrillary tangle are numerous (Hirano et al. 1961). The substantia nigra and locus ceruleus have neuronal loss and neurofibrillary tangles. The basal nucleus and large neurons in the striatum are also vulnerable to neurofibrillary tangle. Biochemically and morphologically, neurofibrillary tangles in Guam PDC are indistinguishable from those in Alzheimer's disease (Buee-Scherrer et al. 1995; Morris et al. 1999).

TDP-43-Related Parkinsonism

In addition to α -synuclein and tau, a third major protein has been found to accumulate within neurons and glial is a number of neurodegenerative disorders, including amyotrophic lateral sclerosis, frontotemporal lobar degeneration (FTLD), Alzheimer's disease and even some parkinsonian disorders. This protein is termed TDP-43 after TAR DNA binding protein of 43-kDa molecular weight, a protein originally found to bind to an HIV transactive response DNA binding protein. It is now known to be an RNA/DNA binding protein that has a number of functions, not all of which are currently known (Buratti and Baralle 2010). It is normally a nuclear protein and its accumulation in cytoplasmic inclusions is decidedly abnormal.

Frontotemporal lobar degenerations are clinically and pathologically heterogeneous, and importantly fall into two major classes—TDP-43 proteinopathies and tauopathies (Mackenzie et al. 2010). In some classification schemes, CBD and PSP are included among FTLD-tau, although as noted above frontal lobe clinical features in both CBD and PSP may be overshadowed by atypical parkinsonism in individual

cases. On the other hand, parkinsonism is often a minor component of FTLD-TDP. Nevertheless, in autopsy series of atypical parkinsonism some cases will inevitably have pathology of FTLD-TDP. These patients often present with mixed clinical syndromes: dementia with parkinsonism, parkinsonism-plus syndrome, or corticobasal syndrome (Josephs et al. 2007). Pathologic findings will be those of FTLD-TDP—focal cortical atrophy with neuronal loss, gliosis, spongiosis, and neuronal inclusions of TDP-43—with the additional findings of significant neuronal loss in the substantia nigra associated with TDP-43 neuronal inclusions. In many cases, there is also TDP-43 pathology in the basal ganglia, which may contribute to the movement disorder.

CONCLUSIONS

Parkinsonian disorders are increasingly classified according to underlying molecular pathology (Dickson et al. 2009), with α -synucleinopathies (PD, MSA) and tauopathies (PSP, CBD, Guam PDC, CTE) being the most common. Recently, another category has been recognized—Parkinsonism associated with TDP-43 proteinopathy. As genetic and molecular studies are increasingly used to further refine underlying disease processes, it is likely that other molecular forms of Parkinsonism will be identified. Currently, the one feature that unifies Parkinsonian disorders is nigrostriatal dopaminergic degeneration, but intriguing evidence from genetic studies (Hoglinger et al. 2011; Nalls et al. 2011) suggest that there may also be shared genetic risk factors (e.g., *MAPT*), but these remain largely unknown at present.

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