Parkinson Disease: Pathophysiology and Histopathological Overview

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ABSTRACT

Parkinson's disease (PD) is distinguished by bradykinesia, stiffness, postural instability, and tremor. The syndrome can be caused by several pathological processes, but the characteristic pathological feature of Parkinson's disease is neurodegeneration accompanied by the presence of α-synuclein neuronal aggregates known as Lewy bodies. LBs and Lewy neurites are insoluble accumulations composed mainly of phosphorylated-synuclein, and they are distributed extensively in both the central and peripheral nervous systems. The distribution of Lewy bodies (LBs) may have a role in determining the phenotype of Lewy body dementia (LBD). Common misdiagnoses for ailments that are pathologically similar include Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome, multiple system atrophy, frontotemporal lobar degeneration, Creutzfeldt-Jakob disease, cerebrovascular illnesses, and essential tremor. This study examines the progression of pathology in cases of accidental and symptomatic Parkinson's disease, proposing a staging technique that is based on the easily identifiable spatial distribution of the lesions.

1. Introduction

Parkinson's disease (PD) is a progressive neurological disorder marked by slow movement, involuntary shaking, stiffness, and difficulty maintaining balance. The presence of certain clinical signs can indicate the occurrence of other disorders, collectively referred to as "Parkinsonism." Parkinsonian disorders are characterized by the prominent presence of Parkinsonism. Various etiological factors, such as degenerative, vascular, traumatic, or toxic factors, might give rise to Parkinsonian disorders. The most commonly observed neurodegenerative causes of Parkinsonism in postmortem studies are synucleinopathies, such as Lewy body disease (LBD) and multiple system atrophy (MSA), as well as tauopathies, including progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). The primary protein that builds up in deteriorating neurons and glia characterizes these illnesses. Due to the presence of other clinical symptoms, such as autonomic dysfunction in MSA, vertical gaze palsy in PSP, and higher-order cortical abnormalities in CBD, some of these conditions are classified as atypical Parkinsonian diseases.1-4

Parkinson disease definition

Although cerebrovascular disease is rare, it can sometimes be accompanied by Parkinsonism, specifically known as "vascular PD" (VaP), which
primarily affects the lower body. The characteristic of all degenerative parkinsonian diseases, whether inherited or spontaneous, is the degeneration of dopaminergic neurons in the substantia nigra that connect to the basal ganglia. The ventrolateral cell groups in the substantia nigra, known as the nigrostriatal pathway, exhibit higher sensitivity compared to the dorsal and medial cell groups, which are part of the mesolimbic pathway and display more resistance. The susceptibility of dopaminergic neurons to selective damage can be attributed to their pacemaker-like characteristics, which lead to frequent fluctuations in intracellular calcium levels. A9 neurons may exhibit less efficacy in calcium buffering compared to A10 neurons, leading to cellular stress and ultimately disrupting cellular homeostasis. Cell death is associated with the disintegration of the nuclear membrane and the liberation of proaggregant nuclear components, such as histones, which can induce synuclein aggregation. Upon the initiation of aggregation, it has the potential to propagate to other cells through direct or indirect means.\(^5\text{,}^6\)

MSA, or multiple system atrophy, shares similarities with Parkinson's disease as it is also a synucleinopathy. However, it is distinct in terms of pathology, as the primary pathogenic changes occur in oligodendroglia rather than neurons. Neuronal inclusions are present; however, they do not bear resemblance to Lewy bodies, and their distribution significantly varies from that observed in Parkinson's disease. The presence of MSA neuronal inclusions is predominantly observed in the putamen, pontine nuclei, and inferior olivary nuclei. Inclusions are present in the substantia nigra and locus ceruleus, although they seldom resemble Lewy bodies. In multiple system atrophy (MSA), the posterolateral putamen shows visible shrinkage and changes in color. There is also a significant loss of neurons and an increase in glial cells, along with an excessive buildup of iron. This iron accumulation is particularly pronounced in the MSA-P subtype, in contrast to Parkinson's disease (PD), where the basal ganglia appear normal in shape and structure, even when there are a substantial number of Lewy neurites present. Observation of putaminal changes is possible when antemortem neuroimaging is performed as part of the diagnostic assessment. MSA-P, in contrast to cerebellar ataxia, is the form of MSA that mostly presents as a Parkinsonian syndrome (MSA-C).\(^6\text{,}^7\)

The clinical misinterpretation of autopsy-confirmed Multiple System Atrophy (MSA) cases most commonly occurs as progressive supranuclear palsy (PSP) in 47% of cases or as atypical Parkinson's disease (PD) in 34% of cases. Parkinson's disease (PD) or dementia with Lewy bodies, both characterized by significant autonomic dysfunction, are the most frequently misdiagnosed conditions in clinical practice that do not exhibit MSA pathology upon autopsy. As medical professionals gain a deeper understanding of the widespread impact of synuclein pathology in Parkinson's disease, which affects both the central and peripheral autonomic nervous systems, it becomes increasingly important to differentiate between Parkinson's disease (PD) and multiple system atrophy (MSA) using criteria that go beyond autonomic dysfunction.\(^5\text{,}^8\)

**The presence of Lewy bodies and Lewy-related pathology in Parkinson's disease (PD)**

Lewy bodies consist of clumps of synuclein that are found inside neurons. Conventional histologic methods only detect a small portion of fully developed inclusions. Immunohistochemistry for synuclein detects the presence of Lewy bodies in susceptible neurons located in specific regions such as the substantia nigra, raphe nuclei, mesopontine tegmentum, locus ceruleus, basal nucleus of Meynert, and dorsal motor nucleus of the vagus. Additionally, it reveals faintly stained inclusions in less susceptible neuronal populations, such as those in the AM. Pre-inclusions, sometimes referred to as cortical-type Lewy bodies, are lesions that seem pale in color and have indistinct boundaries. In Parkinson's disease (PD), there is the presence of atypical synuclein in cellular extensions, particularly in axons, which are frequently referred to as Lewy neurites. The most prevalent type of aberrant synuclein is found amid neurites, particularly in certain brain regions such as the basal ganglia. In these cases, there are usually few or no Lewy bodies present.\(^9\text{,}^10\)
Although the primary location of synuclein immunoreactive pathology in Parkinson's disease is within neurons, oligodendroglial inclusions can also be found in the midbrain and basal ganglia in some cases. The defining feature of MSA is the presence of many oligodendroglial cytoplasmic inclusions (GCI), while early-onset PD is associated with increased glial inclusions as a result of genetic alterations in the synuclein gene. The presence of synuclein in cytoplasmic inclusions implies an aberrant distribution of this protein, which is typically found in presynaptic terminals and plays a role in the release of synaptic vesicles. The presence of abnormal synuclein in Parkinson's disease exhibits pathological modifications after protein synthesis, such as phosphorylation, truncation, and oxidative degradation. Additionally, it adopts an abnormal structure resembling amyloid, which facilitates its aggregation.11,12

The types of Lewy bodies (LBs)

LBs can be classified into two types: brainstem (classical) LBs and cortical LBs. Brainstem-type Lewy bodies (LBs) can be observed through light microscopic analysis of hematoxylin and eosin (HE)-stained sections. These LBs appear as intracytoplasmic structures, either single or numerous, with spherical or elongated shapes. They have eosinophilic cores and are surrounded by peripheral halos. Antibodies targeting phosphorylated-synuclein exhibited strong immunostaining of Lewy bodies (LBs), with the highest concentration of staining observed in the outer region and surrounding area of the central core of brainstem-type LBs. The substantia nigra, locus coeruleus, dorsal vagal nucleus, nucleus basalis of Meynert, and hypothalamus are regions that exhibit a higher propensity for brainstem-type Lewy bodies.13,14

Cortical Lewy bodies (LBs) exhibit eosinophilia; however, they possess irregular and indistinct characteristics, lacking a distinct halo or central core. Cortical Lewy bodies are present in the small neurons located in the deep regions of the amygdaloid nucleus, parahippocampal gyrus, cingulate cortex, and cerebral neocortex. Phosphorylated-synuclein staining in cortical LBs appears to be spread out and not concentrated in specific areas. Spinal cord Purkinje cells and anterior-horn cells rarely exhibit cytoplasmic-synuclein clumps. Lewy bodies (LBs) of the brainstem and cortex types are both made up of randomly placed filaments and circular shapes. However, the cortex-type LBs have fewer circular profiles compared to the brainstem type. The outer ring of LBs consists of filaments that are arranged in a radial pattern. These filaments are more randomly distributed in the cortical type compared to the brainstem type. While it is established that synuclein is found in the thread-like formation of LBs, the primary molecular constituent of the circular formations in the central core remains unidentified.2,13,15

All individuals with accidental instances and clinically evident sporadic PD had synuclein-immunoreactive Lewy neurites (LN)s and Lewy bodies (LBs), even though they did not have intracytoplasmic inclusions often seen in non-PD synucleinopathies. The concurrent AD-related pathology falls within the expected ranges for the age groups. Lipid bodies (LBs) are commonly seen in the form of spherical or reniform structures. They have a somewhat acidophilic nature and exhibit smooth surfaces. Individual LBs or clusters of them are frequently seen in the accumulations of lipofuscin or neuromelanin granules in the affected nerve cells, and they are not observed in Nissl substance patches. At times, poorly defined and weakly immunopositive "pale bodies" develop either between the pigment deposit and the cell nucleus or adjacent to an LB. Thick lymph nodes have a structure like that of a club or a corkscrew. Some are little and stubby, whereas others are elongated and filamentous. Lymph nodes (LN)s have the potential to develop varicose conditions, and both thin and larger LN s have a tendency to routinely divide into two branches, often leading to the formation of teardrop-shaped enlargements. The extent of Parkinson's disease-related pathology varies among cases, ranging from a single LN (+) in the dorsal IX/X motor nucleus to extremely high concentrations of inclusion bodies (+++) in different locations, including the cerebral cortex. The disease causes damage to certain neuronal
types inside particular nuclear grays, as well as specific regions and layers of the cortex. The susceptible types of nerve cells display systematic variations in their propensity to form LNs or LBs.\textsuperscript{14} The presence of lesions in the dorsal IX/X motor nucleus and/or intermediate reticular zone, as well as the anterior olfactory nucleus, is frequently observed in patients with mild symptoms. Our findings indicate that the cerebral cortex is not affected in our sample, as there are no lesions detected in the brain stem. Brain stem lesions in slightly afflicted cases are exclusively limited to the medulla oblongata and pontine tegmentum. Cases exhibiting moderate involvement display additional lesions in certain mesencephalic and prosencephalic nuclei, while all cases with severe disease exhibit degeneration of the neocortex.\textsuperscript{9,10}

For a long time, it has been acknowledged that Lewy-related pathology in Parkinson's disease spreads outside the substantia nigra. However, Braak and his colleagues were the pioneers in categorizing this progression into a coherent stage plan. The onset of neuronal disease initiates in the dorsal motor nucleus of the vagus in the medulla and the anterior olfactory nucleus in the olfactory bulb, subsequently affecting the neurons in the locus ceruleus in the pons and the dopaminergic neurons in the substantia nigra. In advanced stages, the pathology extends to the basal forebrain, amygdala, and medial temporal lobe regions. The convexity of the cortical areas is affected in the last stages. Multiple inquiries have substantiated the validity of the Braak PD staging approach, but there may be occasional instances that deviate from the established framework. For instance, it is possible to observe activity in the substantia nigra without any apparent involvement of the vagus dorsal motor nucleus. Later versions of the Braak scheme suggested that damage to peripheral autonomic neurons, autonomic ganglia, and central autonomic neurons in the spinal cord may occur prior to the impairment of dorsal motor neurons in the vagus. The Lewy-related pathology in the basal ganglia manifests in the later stages of the disease's course.\textsuperscript{14}

At autopsy, many patients have extensive (widespread) or at least involving the limbic system (transitional) Lewy-associated disease, as indicated by the previous description of pathological findings in clinically diagnosed PD (without dementia). The subsequent cases are consistent with the Braak PD stage. Less than one-third of Parkinson's disease (PD) participants with Lewy-related pathology exhibited brainstem dominant Lewy body dementia (LBD) in this limited autopsy collection. Although cases of BLBD are expected to have a low probability of developing dementia with Lewy bodies (DLB) syndrome, which is characterized by Parkinsonism, hallucinations, dream enactment behavior, and fluctuations, the majority of TLBD or DLBD patients are predicted to have an intermediate to high likelihood of becoming DLB. Further investigation is necessary to identify the essential components for modifying the clinical condition and developing clinically evident neurocognitive impairment. However, a clear difference between this group of Parkinson's disease (PD) patients without dementia and those who undergo autopsy with dementia with Lewy bodies (DLB) is the relatively low presence of Alzheimer's disease pathology in the PD without dementia cohort. The median Braak neurofibrillary tangle stage was II out of VI, and the median Thal amyloid phase was 2 out of 5. Individuals who experience significant cognitive deficits are likely to have a higher occurrence of concomitant Alzheimer's disease pathology.\textsuperscript{10,11}

2. Conclusion

The current criteria for neuropathological diagnosis of sporadic Parkinson's disease only enable the differentiation between clinically evident instances and a diverse group of poorly defined cases with less pronounced brain involvement (incidental cases). Therefore, it is necessary to develop a neuropathological staging method that effectively distinguishes between the initial, intermediate, and advanced stages of Parkinson's disease-related lesions. Moreover, employing such a technology will enable the accurate detection of individuals who do not have any PD-related abnormalities.
3. References


