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# A Short Note on Pathology of Parkinson's Disease

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## About the Study

Parkinson's disease is a relatively common worldwide, age-related neurodegenerative disorder. While the movement disorder of Parkinson's disease comprising bradykinesia, tremor, postural instability and gait disturbances is widely recognized in practice, many people living with Parkinson's disease have non-motor symptoms related to damage to multiple neuronal circuits. For example, autonomic dysfunction may occur early in the disease course while many people with Parkinson's disease develop cortical dysfunction such as dementia at later times than the classic movement problems. Thus, Parkinson's disease is a multisystem progressive disorder and at the time of writing is treated only symptomatically.

An important question, both in terms of understanding the clinical disease and for the neuroscience of Parkinson's disease brain, is what the underlying molecular mechanisms of disease risk are. As will be outlined later, current thinking suggests that the overall disease risk is influenced by both genetic and non-genetic mechanisms, of which the latter include age and stochastic events. However, to delineate risk requires some definition of the disease of interest. Therefore, before discussing how we think Parkinson's disease develops and the underlying cellular and molecular events involved in its progression, it is important to describe the underlying brain pathology, which involves protein deposition and neuronal cell death.

## Protein deposition

Postmortem examination of the brain from a person who had lived with Parkinson's disease reveals intraneuronal structures that stain positive with eosin, pathology described by the first studies. Over time, additional ways to label these Lewy bodies have been developed, including antibodies against ubiquitin or several other protein components and lipids. However, the most reliable markers to date are antibodies against α-synuclein which label lewy bodies and Lewy neurites in neurons.

In contrast to the pathological accumulation in cell bodies, α-synuclein is normally concentrated at synaptic vesicles in neurons. Thus, the presence of Lewy bodies and Lewy neurites represent both a loss of normal α-synuclein in Lewy bodies has altered biochemical properties in which the protein is heavily aggregated and organized into fibrils that have strong beta-sheet structure. This is in contrast to the unfolded protein found in solution, the helical form associated with membranes or tetramers in the cellular milieu. Lewy bodies are therefore evidence of protein aggregation in Parkinson's disease.

α-synuclein positive Lewy bodies and Lewy neurites are found throughout many regions of the Parkinson's disease brain. Seminal work identified that Lewy bodies are often found in deep brain structures and the olfactory bulb. Additionally, when Lewy bodies are found in substantia niagra, part of the mid-brain that projects to the striatum and is critical for initiation and termination of movement, they are usually also in deeper brain structures. Equally, if Lewy bodeis are found in the cerebral cortex, they are usually in midbrain and deeper structures. Thus infer that there is a progression of Lewy body pathology from lower brain regions through the midbrain, then with progressive involvement of the cerbral cortex. The staging scheme might approximately correspond to premotor Parkinson's disease, motor Parkinson's disease and Parkinson's disease with dementia. It should be noted that the cross-sectional nature of these studies precludes any direct observation of true progression from region to region in a longitudinal sense within the same patient. Nevertheless, the staging scheme is important for both classifying Parkinson's disease brains and in generating hypotheses about disease progression.

## Neuronal loss

As well as Lewy bodies and Lewy neurites, the classic neuropathological event in Parkinson's disease is loss of neurons in the substantia nigra pars compacta that use dopamine to transmit signals to medium spiny neurons in the striatum. Dopamine neurons in the substantia nigra contain pigment called neuromelanin and because the loss of neurons is substantial in Parkinson's disease, depigmentation can be seen macroscopically in the Parkinson's disease brain.

The loss of dopamine is particularly important in Parkinson's disease for two reasons. First, one of the primary functions of the nigrostriatal pathway is to control initiation of movement. Therefore, loss of nigral neurons leads to at least some of the clinical signs of Parkinson's disease. Second, replacing dopamine by treating with the precursor L-DOPA remains a primary treatment for most Parkinson's disease patients. However, as mighty be expected given that there are nonmotor symptoms in Parkinson's disease, there is also evidence for neuronal damage outside of the nigrostriatal system. For example, loss of several neurotransmitters can be imaged in multiple brain regions throughout the course of Parkinson's disease. How neuronal loss and accumulation of α-synuclein pathology relate to each other as the disease progresses is not always clear. However, it is important to note that the cells with Lewy pathology are not those that have been lost. Therefore, whether Lewy bodies mark cells susceptible to cell death or are instead protective is uncertain.

In summary, there are two major parts to the neuropathology of Parkinson's disease and related disorders, namely, a protein deposition disorder that centers on α-synuclein and changes in cellularity in many brain regions, but prominently including loss of dopamine neurons in the substantia nigra and reactive gliosi. The central argument is that these events are linked and that the identification of genetic contributors to risk of Parkinson's disease is critical in understanding the underlying cellular mechanisms. Therefore, further research is necessary to study some of the critical genes involved in Parkinson's disease.