REVIEW

Milestones in Parkinson's Disease—Clinical and Pathologic Features

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ABSTRACT: The identification of the widespread deposition of fibrillized α-synuclein in Lewy bodies and Lewy neurites in the brains of patients with Parkinson's disease in 1997 has had a profound impact on how the disease is now conceptualized. The previous focus on the loss of the dopaminergic nigrostriatal system, the concept of subcortical dementia, and the idea that Parkinson's disease was dominated by motor impairment have all given way to research assessing more diverse brain regions, clinical symptoms, and phenotypes. It is now recognized that Parkinson's disease is more than just a loss of midbrain dopaminergic neurons in association with Lewy bodies. There are now several theories on how the disease develops and progresses currently being validated in a variety of studies, although many of these theories have yet to incorporate the phenotypic clinical and pathological changes associated with age. A particularly exciting new area of research involves the cell-to-cell transmission of pathogenic proteins. The recent consensus definition of Parkinson's disease dementia will allow its pathologic substrates to be determined. These advances have progressed to a stage where the preclinical stages of Parkinson's disease and its specific signs and symptoms are being predicted and tested clinically. Such strategies herald a future wave of preventive strategies for Parkinson's disease and its clinical symptoms. © 2011 *Movement* Disorder Society

Key Words: α-synuclein; Lewy bodies; neuropathology; preclinical Parkinson's disease

Parkinson's disease (PD) is an inexorably progressive neurological disease that leads to increasing physical handicap as a result of a very specific disturbance of movement, usually referred to by clinicians as bradykinesia, which is characterized by slowness of initiation of voluntary movement with a progressive reduction in speed and amplitude of sequential motor tasks. This difficulty can be improved substantially in most cases by L-dopa therapy, albeit with the risk of developing drug-induced involuntary movements. There are as yet no reliable biomarkers, but PD can be distinguished from atypical and secondary causes of parkinsonism on clinical grounds. Pathological confirmation hinges on the finding of severe selective loss of pigmented neurons in the ventral tier of the substantia nigra with the presence of Lewy bodies and Lewy neurites in specific regions of the nervous system.[1]

For many years after James Parkinson's clinical description of the shaking palsy in 1817,[2] the pathological substratum associated with the disorder remained elusive, and even after Lewy bodies and cell loss had been identified by morbid anatomists, the importance of the substantia nigra lesion was not generally acknowledged until the 1950s.

In the first 2 decades after the discovery of nigrostriatal dopamine denervation in PD, there was an emphasis on neurotransmitter/neuropeptide systems, with considerable knowledge of receptor differentiation and their pharmacologic properties.[3] The now-outdated concept of subcortical dementia emerged, in which pathology sparing the cortex and concentrating in the thalamus, basal ganglia, and related forebrain and

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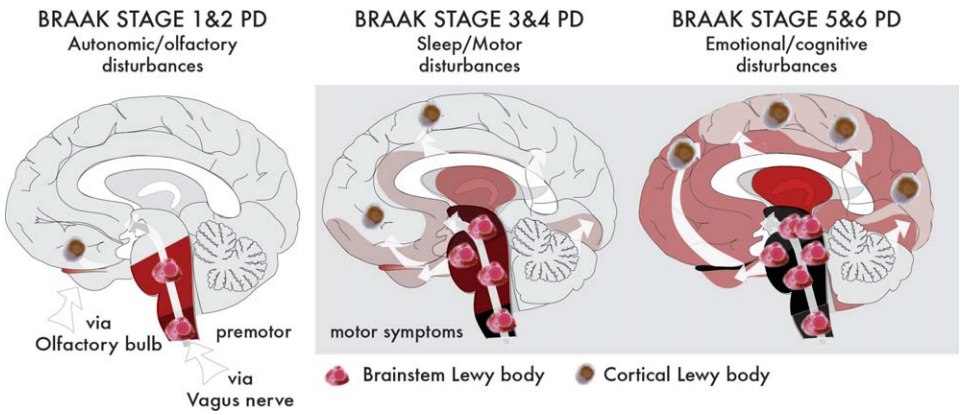

FIG. 1. Stylized representation of the Braak staging for Parkinson's disease showing the initiation sites in the medulla oblongata and olfactory bulb through to the later infiltration of Lewy pathology into the cortical regions.

brainstem nuclei was considered to cause cognitive impairment, particularly deficiencies in arousal, attention, mood, motivation, language, memory, abstraction, and visuospatial skills.[4] The main revelations since this time have been the identification of the primary proteins and cellular mechanisms involved in the neuropathological process (largely following from genetic research), and a recognition of the extensiveness and progression of neuropathology throughout the nervous system.

PD Is More Than Just Loss of Midbrain Dopamine Neurons in Association with Lewy Bodies

Research in the last 25 years has confirmed that although the lesion in the substantia nigra remains a sine qua non for the pathological confirmation of the disease, the pathological lesions are much more extensive and involve a number of ascending projection pathways in the brainstem and areas of the neocortex.[5,6] Although the pathology of PD affects a variety of neuronal systems, it does not cause substantial brain tissue loss[7,8] because cell loss is restricted to only certain neuronal populations within any anatomical brain region, including the substantia nigra.[9] We now know there is substantial and early neuronal loss in other regions involved in motor control (presupplementary cortex[10] and caudal intralaminar thalamus[11]) and in the A10 neurons of the mesocortical system.[12] The involvement of other neuronal populations occurs late in PD or in certain clinical phenotypes and includes neuronal loss in the cholinergic basal forebrain and mesopontine systems,[13] in the hypothalamic hypocretin system,[14,15] and in the upper brainstem serotonin system.[16] In many other regions concentrating Lewy bodies, there is very limited neuronal loss, including the amygdala,[17] dorsal motor nucleus of the vagus nerve,[18] locus coeruleus,[19] and neocortex.[20] The major symptoms associated with PD seem to appear following significant cell loss, possibly reflecting neuronal compensation.[21]

Although cell loss is restricted, even in end-stage cases with PD, there is now a much greater appreciation of the more widespread presence of Lewy neurites and Lewy bodies composed of aggregates of α-synuclein in PD. This is due to the seminal work of Heiko Braak and colleagues, who developed a theory for the progression of PD from people with Lewy pathology but without clinical features to those with full-blown end-stage clinical disease.[22,23] Although many groups had published that Lewy pathology was widespread in PD, with some even publishing on preclinical incidental Lewy body disease,[24,25] the more fully developed concept of pathological progression developed by Braak and collegues allowed a framework of disease progression with clinical resonance to be developed.[26,27] The theory is that Lewy pathology progresses through cell-to-cell contact from the periphery into the medulla oblongata and olfactory system, causing autonomic and olfactory deficits, and then further infiltrates into the brainstem, causing sleep and motor disturbances, then to the limbic system and finally neocortical regions, causing neurobehavioral and cognitive impairment (Fig. 1). Recent studies demonstrating that misfolded α-synuclein can be transferred across synapses and spread within postsynaptic cells[28] lends credence to the concept of cell-to-cell transfer. The most contentious aspect of the Braak staging of PD is identifying where the Lewy pathology begins in the brain. Although a number of studies assessing cases with clinical PD broadly support the concepts developed by Braak and colleagues once the disease has begun,[18,29–31] other studies on similar populations suggest that the 7%–8% of patients where no medullary Lewy bodies were found in 1–3 thin sections negates this concept.[32,33] A recent careful analysis of the degree of medullary pathology in PD confirmed that α-synuclein deposition is relatively consistent in clinical PD

(including those with *LRRK2* mutations), but that the severity of pathology is independent of the degree of Lewy pathology occurring in later stages and does not relate to cell loss in the medulla oblongata or other regions.[18] In prospectively studied cases with typical PD, the slow progression through the predicted Braak stages is observed and only modified by the age of symptom onset (faster progression with older age) and degree of age-related Alzheimer pathology (widespread, more rapid progression).[34] The criticism that many elderly without the clinical features have widespread α-synuclein deposition consistent with late Braak stages[35] presupposes that Lewy pathology only occurs in clinical PD. The realization that Lewy pathology occurs with a different pattern in most patients with Alzheimer's disease,[36,37] as well as in dementia with Lewy bodies, needs to be factored into such evaluations. The lack of correlation between Braak staging and clinical severity has also been seen as problematic,[35] but as stated above, the clinical deficits of PD appear to be more related to the degree of cell loss rather than to the severity of Lewy pathology. Fluctuations and dysfunction may relate more to Lewy pathology in the absence of cell loss, and these will be assessed in further detail below. Overall, there is considerable data supporting the pattern of Lewy pathology in PD proposed by Braak and colleagues (but not its severity or relationship to cell loss), although there is also considerable evidence to suggest a diversity of clinical syndromes can diverge from asymptomatic cases with Lewy pathology.

PD Progression

A variety of different types of studies indicate that PD is slow in progressing through the nervous system, with restricted pathology occurring prior to symptom onset. In fact, the onset of PD is so gradual that it is often difficult to pinpoint in an individual patient when the disease first emerges, and by the time the diagnosis is made, pathology is likely to be widespread (see above). Many of the earliest motor symptoms are misinterpreted as loss of elasticity due to aging, rheumatism, or depression, and other suggestive prodromal symptoms such as fatigue, autonomic dysfunction manifested by constipation, temperature dysregulation and excessive perspiration, or sleep disturbances are insufficient in isolation to make a definitive diagnosis.

Braak's suggestion that the disease process may start peripherally and spread to the olfactory pathways and medulla oblongata has led to interest in the possibility that autonomic disturbances and hyposmia may be clinical correlates of Lewy body deposition in these regions.[26,27] There is also increasing support for the notion that early intervention with disease-modifying therapies will be essential if a significant impact is to be made on the natural history of the disorder. The possibility that some of the more specific nonmotor symptoms that can be seen early in the course of PD might be predictors for the development of PD has led to a great deal of recent research.

Although smell loss was recognized as a feature of PD in the mid-1970s,[38] it was not until the mid-1980s that olfactory function began to be studied in more detail in PD. It was even later that the pathological substrate was identified as Lewy bodies and neurites in the olfactory bulb and its projections through the olfactory tract to the anterior olfactory nucleus.[22,39,40] Developed by Doty and colleagues, the University of Pennsylvania Smell Identification Test (UPSIT) has been used extensively to characterize smell loss in PD and related disorders,[41] with clinical studies demonstrating loss of olfactory function in PD regardless of stage or duration of PD.[42] Further, hyposmia is present in at least 80% of patients with PD but is much rarer in multiple system atrophy or progressive supranuclear palsy.[43] These studies support the very early preclinical loss of olfactory function in PD.

Constipation is very common in PD. The dorsal motor nucleus of the vagus nerve provides parasympathetic innervation to the visceral organs including the stomach and intestines and is consistently affected with neuritic pathology in PD.[44] Further, patients with PD have delayed colon transit time that may be the consequence of Lewy bodies in degenerating nerve cells within Auerbach's and Meissner's plexuses in the gut.[45] Routine colonoscopy biopsies recently have been shown to be a useful tool for a premortem neuropathological diagnosis of PD with the amount of pathology correlating with constipation.[46] Pathologic involvement of the lower GI tract may not only be a characteristic finding but, more importantly, may be an early hallmark of the disease. For example, in the Honolulu-Asia Aging Study, subjects with less frequent daily bowel movements were more likely to have incidental Lewy bodies at autopsy.[47]

Cardiac involvement in PD has also generated interest as a target of α-synuclein pathology. Cardiac sympathetic fibers are decreased in PD, and abnormal accumulation of α-synuclein and reduced MIBG uptake are detected in the myocardium and epicardium.[48–50] Lewy bodies have even been detected in the myocardium, sinoatrial node, and sympathetic ganglia.[51,52] As with the GI tract and olfactory structures, there is now evidence that α-synuclein pathology of the heart may predate the onset of neurologic symptoms, as recent studies have demonstrated α-synuclein aggregates in the myocardium in cases of incidental Lewy body disease.[50] Despite early pathologic involvement, it is noteworthy that significant autonomic symptoms in PD are a feature of advanced disease, suggesting a long latency between the initiation of

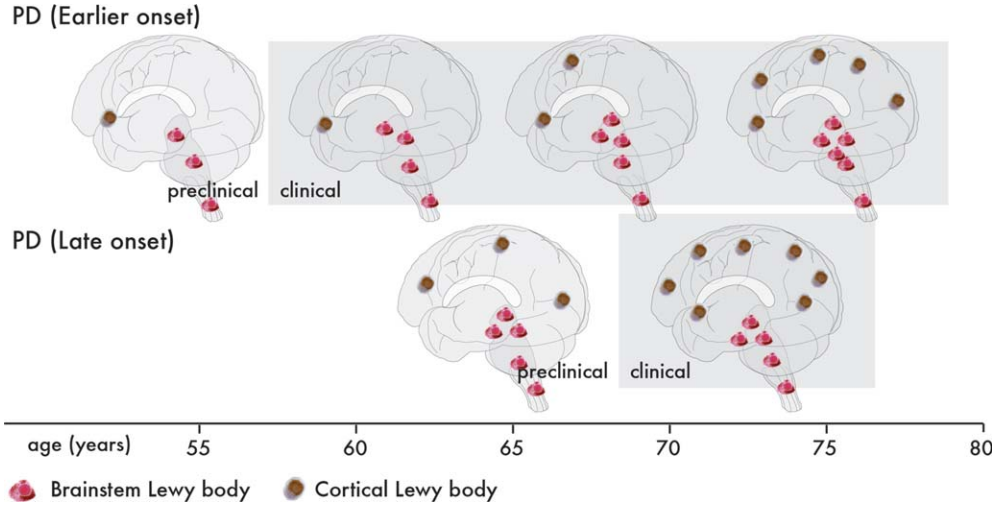

FIG. 2. Stylized representation of the different rates of Lewy pathology infiltration depending on the age of onset of Parkinson's disease.

neuritic pathology and clinical symptoms. The exception may be heart rate variability, which is lower in PD patients and is currently being studied as a potential marker of early PD.[53,54] Although relatively specific for Lewy body disorders, cardiac sympathetic denervation does not consistently correlate with disease duration or severity and does not correlate with clinical dysautonomia.

REM sleep behavior disorder (RBD) is characterized by the enactment of action-filled dreams with vigorous motor and vocal activity that can be injurious. There appears to be a connection between RBD and α-synucleinopathies, and this may be an early feature of both PD and multiple system atrophy. Studies have demonstrated that PD may develop some years after the onset of RBD[55] and that many patients with RBD have reduced heart rate variability, as predicted by Braak staging.[53] There may also be a relationship between the severity of RBD and the eventual development of PD.[56] The neuropathologic substrate of RBD is not definitively established, although postmortem examination of RBD patients without motor signs has shown gliosis, neuronal loss, and even Lewy bodies in the locus coeruleus and substantia nigra.[57,58] It is also possible that in PD patients with RBD, neuropathological changes in brainstem cholinergic nuclei are responsible.[59]

Once diagnosed with the motor symptoms of PD, the rate of disease progression differs depending on the age of symptom onset, with an older age of onset causing a more rapid disease course (Fig. 2).[60,61] In tremor-dominant patients with onset between 50 and 70 years of age, the disease course is usually very slow, with Lewy pathology reaching limbic regions on average 13 years after symptom onset and taking another 5 years to reach cortical regions (Fig. 2).[29] As noted above, the further infiltration of Lewy pathology into more brain regions and more neurons within each region occurs largely without substantial cell loss until late in the clinical course. Confirmation of a slow infiltration of Lewy pathology has been shown in therapeutic fetal transplants in patients with typical PD, where grafted neurons start to demonstrate Lewy pathology only after 10 years of transplantation.[28] These findings have stimulated new research and ideas on how Lewy pathology slowly invades the different vulnerable sets of neurons in patients with PD.

A proportion of normal elderly individuals have Lewy pathology in the brain (preclinical or incidental Lewy body disease[62–67]). In addition, there is evidence for the preclinical loss of neurons.[30,64] For cell loss, evidence suggests that nigral degeneration starts at least 5 years prior to symptom onset.[9,68] Although overt cell loss is not considered a feature of incidental Lewy body disease, quantitative studies show a 50% loss of the dopamine structures in the striatum of cases with incidental Lewy bodies compared with controls,[30,64] consistent with a similar timing for the development of brainstem Lewy pathology and the targeted neuronal degeneration of PD.

Pathological Substrate of Dementia in PD

Over the last 25 years the clinical syndrome of dementia with Lewy bodies has been developed, in which Lewy pathology occurs in a dominant dementia setting and patients may or may not also have parkinsonism.[69,70] For the majority of such patients, the amount of neuritic Alzheimer-type pathology rather than Lewy pathology correlates with dementia severity.[71,72] In addition, amygdala Lewy pathology occurs in nearly all patients with pathological Alzheimer's disease,[73] making this syndrome the dominant Lewy pathology syndrome. This finding has necessitated modifications to diagnostic criteria and disease-staging schemes[37,74] and has implications for assuming all

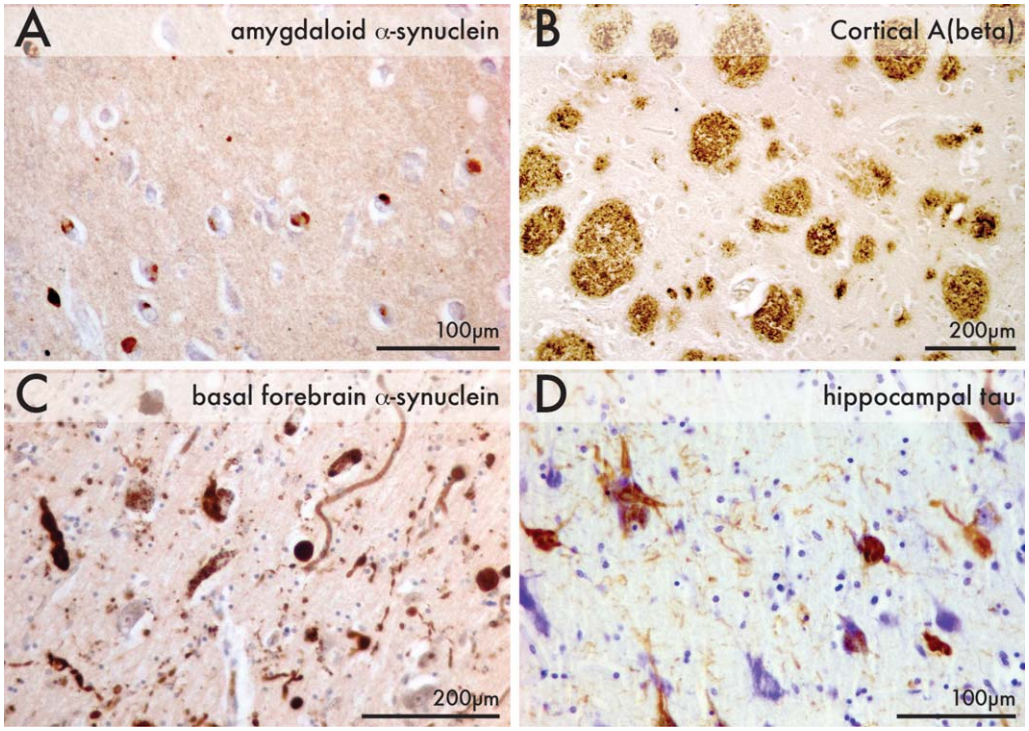

FIG. 3. Examples of the various pathologies contributing to dementia in different types of patients with Parkinson's disease.

incidental Lewy body disease cases are preclinical PD, especially as a relatively large number of clinically normal elderly have some cortical rather than subcortical Lewy pathology.[65] Although there is still enormous difficulty in separating dementia cases with restricted versus rampant Lewy pathology and estimating the degree of Alzheimer versus Lewy pathology, there is no difficulty in separating patients with dominant PD from those with an early dominant dementia phenotype on clinical grounds, especially using the 1-year rule, as recommended by various consortia.[70,75]

Following the clarification of Lewy pathologies associated with dementia, it has generally been assumed that the cognitive changes in PD are always the result of Lewy body infiltration into cortical regions, an assumption incorporated into the Braak staging scheme for PD[23,76] and current diagnostic criteria.[1] However, this seems unlikely to us to be based on the main clinical predictor of age and age-related pathologies for earlier dementia onset in PD.[61,77–80] Pathological confirmation that additional neuropathologies can be associated with dementia in PD are numerous.[81–84] In particular, the earlier the dementia onset in PD, the more likely additional neuropathologies are involved (Fig. 3).[29,61,80] In these studies, the pathologies contributing to earlier dementia in PD include degeneration of cholinergic systems, Aβ plaque deposition, neuritic changes of Alzheimer's disease, and in some cases, diffuse cerebrovascular disease. In patients with a long disease duration where sufficient time for the slow accumulation of Lewy pathology can occur, limbic and cortical Lewy pathology correlates with the presence and severity of dementia in PD.[29,61,85,86] Although Lewy pathology is common in most cases with dementia (see above), the variation in the timing of dementia onset in the course of PD is most often related to the presence of additional intervening neuropathologies.

Future Directions

To develop preventive strategies for PD, more knowledge and understanding are required about the preclinical changes that occur prior to overt motor deficits. The constellation of prodromal nonmotor features seen in some patients, as well as advances in genetics and neuroimaging, offers some hope for identifying individuals at risk of PD. The term *Parkinson's at risk syndrome* (PARS) has been suggested to describe patients who have PD pathologically but have not yet manifested neurologic symptoms.[87] In the PARS study, a 2-stage screening process that begins with olfactory testing and is followed by dopamine transporter imaging is testing the feasibility of screening thousands of "normal" individuals in order to identify a cohort of at-risk subjects who could eventually participate in a clinical trial of PD delay or prevention.[87] In this study subjects are also assessed for RBD, mild motor signs, genomics, and proteomics. Other cohorts focusing on genetic risk such as *LRRK2* carriers, RBD, and abnormal imaging modalities such as MIBG scintigraphy or dopamine transporter imaging are in the early stages of development. These enriched populations will be invaluable in

providing insight into the "nonmotor" stage of PD and could set the stage for trials of PD prevention.

A difficulty that requires some resolution is to determine whether there are similar or different preclinical changes in incidental Lewy body patients who may develop a dominant motor phenotype compared with a dominant dementia phenotype. Determining either the early predictors for these different phenotypes or predictors of subsequent clinical phenotype once Lewy pathology begins may guide preventive therapeutic options.

An active area of research based on recent pathological findings is how Lewy pathology invades the different vulnerable sets of neurons in patients with PD. Developing a greater understanding of the cell types and mechanisms involved in this process also holds promise for developing therapeutic strategies that may be able to halt disease progression.

The recognition that once motor symptoms intervene, progression is more rapid in those with an older age at onset requires further clarification and modeling. Greater understanding of the different rates of progressions may move the treatment of PD further down the road to a more personalized scenario.

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