When Does Parkinson Disease Start?

Rodolfo Savica, MD, MSc; Walter A. Rocca, MD, MPH; J. Eric Ahlskog, PhD, MD

There is convincing evidence that the Parkinson disease neurodegenerative process begins many years before the onset of motor manifestations. Initial estimates based on nigral neuropathological findings or striatal dopamine imaging suggested a 5- to 6-year preclinical period. However, more recent evidence of Lewy body pathology in other neuronal populations preceding nigral involvement suggests that the preclinical phase may be much longer. Epidemiologic studies of nonmotor manifestations, such as constipation, anxiety disorders, rapid eye movement sleep behavior disorder (RBD), and anemia, suggest that the preclinical period extends at least 20 years before the motor manifestations. Olfactory impairment and depression may also precede the onset of motor manifestations; however, the lag time may be shorter. Recognition of a nonmotor preclinical phase spanning 20 or more years should guide the search for predictive biomarkers and the identification of risk or protective factors for Parkinson disease.

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Parkinson disease (PD) is a neurodegenerative disorder that results in progressive extrapyramidal motor dysfunction primarily related to loss of dopaminergic nigrostriatal function. Longevity has substantially improved with dopamine replacement therapy; however, advanced-stage PD motor symptoms respond incompletely to levodopa or related drugs and are now recognized to be caused by nondopaminergic mechanisms. Although the dopaminergic nigrostriatal pathway may still hold clues, research on the causes of PD has now extended beyond this system.

Clues relating to the causes of PD are crucially time dependent because causal factors may surface and disappear at any time during the patients’ lives; however, some component causative factor(s) must be present before the first evidence of PD onset. Thus, dating the true onset of PD is important to properly direct research of predictive biomarkers and risk and protective factors.

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NEUROPATHOLOGIC AND IMAGING DATA

Until recently, the dopaminergic nigrostriatal system has been assumed to be fundamental to PD, and the length of the preclinical phase has been estimated by backward extrapolation from the known rate of nigrostriatal loss from autopsy studies (Table). Extrapolation from series of postmortem brains with Lewy body pathology in the substantia nigra predicted a preclinical stage of approximately 5 years. Similarly, striatal fludeoxyglucose 18 dopamine positron emission tomography studies estimated a 6-year preclinical phase.

However, the studies of Braak and colleagues emphasize that Lewy body pathology is much more widespread than previously acknowledged. The substantia nigra appears to be relatively spared early in the disease course, whereas other regions, including the lower brainstem, olfactory bulb, and autonomic nervous system, are already accumulating Lewy body pathology. Therefore, the previous es-
imates of the PD premotor phase that focused solely on substantia nigra now appear to be gross underestimates. The purpose of this article is to compile clinical and epidemiologic studies that have a bearing on the preclinical phase in PD in order to better estimate the PD timeline.

CLINICAL AND EPIDEMIOLOGIC DATA

Epidemiologic studies have suggested that certain neurologic or psychiatric manifestations may precede the traditional motor manifestations of PD by long periods. In addition, some epidemiologic studies have suggested the occurrence of early manifestations of PD outside the central or peripheral nervous systems (Table).

CONSTIPATION

Symptoms of dysautonomia develop in most patients during the course of PD, and constipation is probably the most common manifestation. Constipation relates to impaired colonic motility and is not simply attributable to medications.21 Previous authors22 have commented that constipation may sometimes precede the initial motor manifestations of PD. This finding was borne out in the Honolulu-Asia Aging Study,23 in which men without PD or dementia were prospectively followed up after completing a bowel-movement questionnaire. Incidental Lewy body pathology was present in nearly one-fourth of individuals with constipation. Incidental Lewy body pathology in the autonomic nervous system of individuals without PD.

Further studies in the Honolulu-Asia Aging cohort allowed estimation of a timeline between constipation and later PD. Thus, men with constipation had a significantly greater risk of subsequent development of PD, and the mean interval from bowel-movement questionnaire to PD symptoms was 10 years (12 years to diagnosis).7 These findings were extended to women by a case-control study in Olmsted County, Minnesota, that showed an association between earlier-life constipation documented in historical medical records and subsequent risk of PD. Importantly, the association remained significant when restricted to constipation documented 20 or more years before the onset of PD motor manifestations.8 In summary, constipation may precede the motor symptoms of PD by at least 10 and perhaps more than 20 years (Table).

ANXIETY DISORDERS

Anxiety is common among patients with PD; it sometimes responds to dopamine replacement therapy.23 Several case-control or cohort studies suggested that anxiety may be 1 of the earliest manifestations of PD. First, in a population-based, case-control study,20 anxiety diagnoses documented in historical medical records were significantly associated with later PD, even when analyses were restricted to 20 or more years before PD. Second, the Health Professionals Follow-up Study9 showed that “phobic anxiety” was a significant risk factor for the development of PD within 4 years. Finally, the Mayo Clinic Cohort Study of Personality and Aging11 showed that patients with high scores on the anxiety scale or the composite neuroticism scale of the Minnesota Multiphasic Personality Inventory had a significantly increased risk of PD. The association with neuroticism remained significant when analyses were restricted to individuals who completed the Minnesota Multiphasic Personality Inventory between 20 and 39 years of age, suggesting pre-existing manifestations well beyond 20 years before PD. In summary, anxiety and neuroticism may predate motor PD by more than 20 years (Table).

RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

Rapid eye movement sleep behavior disorder (RBD) is common in PD and is recognized by clinicians to often precede PD motor symptoms.20 In fact, RBD has been associated with α-synucleinopathies in general, including not only PD but also dementia with Lewy bodies and multiple system atrophy.27 The precise neuroanatomical substrate for RBD has not been identified in humans, but animal studies28 localize it to the region of the pontine subcaeruleus nucleus; this region is at a brainstem level consistent with early Braak stages.17 Patients with isolated RBD have reduced dopamine in the striatum, as shown by imaging.20

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<th>Source</th>
<th>Type of Study</th>
<th>Approximate Length of Premotor Phase, y</th>
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<tbody>
<tr>
<td>Neuropathology</td>
<td>Fearnley and Lees,3 1991 Case-control 5b</td>
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<tr>
<td>Neuroimaging</td>
<td>Morrish et al,6 1998 Clinical series 7b</td>
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<tr>
<td>Constipation</td>
<td>Abbott et al,7 2001 Cohort 10b</td>
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<td>Weisskopf et al,8 2003 Cohort 4c</td>
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aApproximate length of premotor phase, as reported by the authors. For some studies, the number corresponds to the observed mean or median length.
bMean.
cRange.
dNumber of years between RBD and the onset of Parkinson disease in each of the 3 individuals described in the study.
emedian.
In a prospective study,\textsuperscript{12} isolated RBD was found to evolve into PD in 38% of patients, with a mean interval of 12.7 years. Two patients with isolated RBD, without development of PD, underwent autopsy 15 to 20 years later; each was found to harbor Lewy body pathology.\textsuperscript{13,14} Finally, 3 patients with long-standing isolated RBD presented with newly diagnosed parkinsonism and abnormal dopamine brain imaging within 14, 16, and 38 years, respectively.\textsuperscript{15} In summary, RBD may precede PD by 12 years or more (Table).

ANEMIA

Parkinson disease may have systemic correlates outside the central or peripheral nervous systems. For example, peripheral mitochondrial function in platelets,\textsuperscript{38} lymphocytes,\textsuperscript{31} and muscle\textsuperscript{32} is consistently impaired in patients with PD compared with control individuals. However, there is a paucity of studies investigating this or other systemic abnormalities in the preclinical phase of PD.

In a population-based, case-control study, anemia was a significant risk factor for later PD, but only when it was documented long before PD (median, 20 years). The greatest association was with anemia starting 20 to 29 years before PD\textsuperscript{36}; analyses restricted to anemia that occurred more than 30 years before the onset of PD still revealed a significant association (Table). However, this finding requires replication, and anemia may be a risk factor for PD rather than an early manifestation.\textsuperscript{56} Anemia has also been associated with a higher risk of Alzheimer disease.\textsuperscript{33,34}

OTHER EARLY MANIFESTATIONS WITH SHORTER TIMELINES

Olfactory impairment and depression are 2 other non-motor manifestations that have been repeatedly described in the preclinical phase of PD. However, the lag time from the appearance of these manifestations to the onset of motor manifestations of PD has not been studied adequately. The limited studies\textsuperscript{10,11,35,36} available indicate a relatively shorter lag time compared with the manifestations listed in the Table.

In the Honolulu-Asia Aging Study,\textsuperscript{35} olfactory dysfunction was associated with an increased risk of PD; however, the association was significant only for the first 4 years of follow-up. In addition, olfactory dysfunction predicted postmortem Lewy body pathology among individuals who died free of parkinsonism.\textsuperscript{36} Other investigators noted that olfactory dysfunction was significantly associated with subsequent development of PD within the ensuing 2 to 5 years among first-degree relatives of patients with PD.\textsuperscript{37,38}

A number of studies\textsuperscript{39-41} suggest that depression may precede PD motor manifestations. However, studies assessing the interval from the documentation of depression to the onset of motor manifestations of PD suggested that the association becomes insignificant for depression occurring earlier than 2 years,\textsuperscript{42} 5 years,\textsuperscript{43} or 10 years.\textsuperscript{44} In addition, the Mayo Clinic Cohort Study of Personality and Aging failed to reveal an association of high score on the depression scale of the Minnesota Multiphasic Personality Inventory with the long-term risk of PD.\textsuperscript{11}

CONCLUSIONS

The Table summarizes several studies suggesting a relatively long premotor phase of PD. Constipation and anxiety disorders appear to be present in some patients more than 20 years before PD motor symptoms. Anemia may have a similar long preclinical time line; however, it was only documented in 1 population-based, case-control study.\textsuperscript{46} Rapid eye movement sleep behavior disorder precedes typical PD by more than 12 years in many patients. A conservative view would place the earliest evidence of Lewy body PD at least 20 years before the onset of typical motor manifestations. Thus, some initial causative factor or factors must already be present at that time.

It may, however, be overly simplistic to assume there is a continuous evolution from the inception to the full development of PD.\textsuperscript{44} Lewy body neurodegenerative processes may occur in a stepwise fashion, requiring additional causative factors to advance to the next level. In fact, such a noncontinuous evolution seems plausible, given the relative proportions of asymptomatic (incidental) Lewy body pathology vs PD in the general population. Incidental Lewy body disease is found in approximately 10% to 17% of people older than 60 years,\textsuperscript{36,56} which is 5 to 10 times the frequency of PD. Therefore, in some individuals, the pathogenetic process may not advance to the full clinical syndrome without a second (or more) causative factor(s). Thus, the epidemiologic search for the causes of PD must encompass early and later factors (ie, multifactorial and multistage causes).

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