The Relationship of Parkinson Disease With Aging

Gilberto Levy, MD, MS

Twentieth-century hypotheses attributing a substantive role to aging in Parkinson disease (PD) pathogenesis have been countered by evidence from clinical, pathological, and biochemical investigations. However, age influences the clinical progression of PD. Several studies have demonstrated that advancing age is associated with a faster rate of motor progression, decreased levodopa responsiveness, more severe gait and postural impairment, and more severe cognitive impairment and the development of dementia in patients with PD. A model for the relationship between PD and aging is proposed that incorporates the following 3 elements: (1) There occurs a superposition of a topographic gradient of neuronal loss in brainstem and basal forebrain structures related to the disease process and an aging-related temporal gradient. (2) While PD is a chronic progressive disorder, the most important determinant of clinical progression is advancing age rather than disease duration. (3) The effects of the disease process and aging on nondopaminergic structures involve a biologic interaction. The model implies that understanding the degenerative process in nondopaminergic structures in PD as it relates to molecular mechanisms accompanying the aging of the nervous system may create opportunities for interventions affecting the clinical progression of the disease.

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Seldom occurring before the age of fifty, and frequently yielding but little inconvenience for several months, it is generally considered as the irremediable diminution of the nervous influence, naturally resulting from declining life; and remedies therefore are seldom sought for.

James Parkinson, 1817

Although Parkinson disease (PD) has long been perceived as related to aging, 2 prominent hypotheses attributing a substantive role to aging in PD pathogenesis (“accelerated aging” and normal aging-related neuronal attrition following a subclinical environmental insult to the substantia nigra in early or middle adult life) were proposed late in the 20th century. While they had the merit of fostering much research, these hypotheses have subsequently been countered by clinical, pathological, and biochemical investigations showing qualitative differences between patients with PD and healthy elderly subjects. Moreover, the postmortem observation of highly increased markers of recent cell death in the substantia nigra of patients with PD would be consistent with an active pathological process rather than normal aging-related neuronal attrition or accelerated aging.

To propose a model for the relationship between PD and aging that postulates a novel role for aging in PD pathogenesis, I briefly review the influence of age on the clinical progression of PD. Unlike previous hypotheses, the role for aging in PD pathogenesis hypothesized here relates aging to the clinical progression of the disease rather than to clinical onset or disease initiation, and involves an underlying mechanism acting on nondopaminergic rather than dopaminergic structures.
AGE INFLUENCES THE CLINICAL PROGRESSION OF PD

Several studies have demonstrated that age influences the clinical progression of PD. Advancing age is associated with a faster rate of motor progression, decreased levodopa responsiveness, more severe gait and postural impairment, and more severe cognitive impairment and the development of dementia in patients with PD.

Rate of Motor Progression

Cross-sectional studies have suggested that, compared with patients with PD with an earlier onset, those with a later onset have a faster rate of motor progression because of a significantly shorter disease duration in the setting of a similar level of disability and a significantly more severe motor impairment in the setting of a similar disease duration. This has been corroborated by many longitudinal studies showing an association of older age at onset with faster progression of motor signs or disability in patients with PD. For instance, in a population-based longitudinal study, the increase per year in the total Unified Parkinson Disease Rating Scale motor score (range, 0 [normal] – 108 [most severe impairment]) was 2.6 points for patients aged 50 years at onset and 3.8 points for patients aged 70 years at onset.

Levodopa Responsiveness

Soon after the advent of levodopa therapy, Granerus et al reported that the improvement in activities of daily living with levodopa was inversely correlated with age at the start of treatment. Studies assessing response to levodopa with a standardized levodopa challenge have also demonstrated a smaller magnitude of response in older than in younger patients with PD. Gait and postural impairment are relatively refractory to levodopa therapy in the middle and late stages of PD, whereas tremor, rigidity, and bradykinesia respond to levodopa throughout the course of the disease. This supports a role for nondopaminergic lesions in gait and postural impairment in PD and suggests that the association of older age with decreased levodopa responsiveness may be related to an association of older age with more severe gait and postural impairment in PD.

Gait and Postural Impairment

An association of older age with more severe gait and postural impairment in PD has been supported by different studies. In a community-based sample of patients with PD, age at evaluation was significantly correlated with the severity of gait and postural impairment, but not with the severity of tremor, rigidity, and bradykinesia. In a service-based sample with a wide range of disease duration and age, the contribution of age at evaluation to the severity of different motor signs in PD, as measured by additional variability accounted for in linear regression models, was higher for gait and postural impairment (13.6%) than for tremor, rigidity, and bradykinesia (≤5.0%). These findings are consistent with those from a longitudinal study showing that older age at onset was a significant predictor of the development of balance impairment in patients with PD.

Cognitive Impairment and Dementia

Cross-sectional neuropsychological studies have provided evidence that older age at onset is associated with more severe cognitive impairment in patients with PD. In an epidemiologic study, the age-specific prevalence of dementia in PD ranged from 12.4% in the group aged 50 to 59 years to 68.7% in the group older than 80 years. The association of older age with the development of dementia in PD has been confirmed in prospective cohort studies and other longitudinal investigations have also shown an association of older age with faster rate of cognitive decline in patients with PD. Many of these studies have shown that only age at evaluation was significantly associated with faster rate of cognitive decline or the development of dementia when both age at evaluation and age at onset of PD were examined in the analysis, suggesting that current age is a more important predictor of rate of cognitive decline and dementia in PD than age at disease onset.

A MODEL FOR THE RELATIONSHIP BETWEEN PD AND AGING

A first element of the model for the relationship between PD and aging proposed here is as follows: There occurs a superposition of a topographic gradient of neuronal loss in brainstem and basal forebrain structures related to the disease process and an aging-related temporal gradient. This is schematically represented in the Figure. The topographic gradient of neuronal loss as depicted in the Figure (panel A) is supported by quantitative pathological and biochemical investigations comparing the brains of patients with PD with and without dementia and healthy control subjects. In a recent pathological study of brains with incidental Lewy bodies and Lewy neurites detected with α-synuclein immunostaining, Del Tredici et al suggested that α-synuclein inclusions affect lower brainstem structures, such as the dorsal motor nucleus of the vagus and the locus ceruleus, before the substantia nigra pars compacta. A major limitation of this study was that the incidental cases were selected according to the presence of α-synuclein inclusions in the dorsal motor nucleus of the vagus itself, and a sample of 58 brains without α-synuclein inclusions in the dorsal motor nucleus of the vagus were examined to account for the possibility that the substantia nigra pars compacta might be affected earlier on. Two subsequent investigations have reported brains in which α-synuclein inclusions were present in the substantia nigra pars compacta but not in the dorsal motor nucleus of the vagus. Based on the findings of this study and on the assumption that incidental Lewy bodies represent preclinical PD, Braak et al proposed a staging of neuropathological changes in PD. The study by Del Tredici et al did not involve quantitative assessments of neuronal count and the staging procedure proposed by Braak et al specifically tries to account for the progression in the distribu-
was not. In a prevalence study, patients with PD and balance impairment at baseline, while disease duration development of balance impairment among patients without patients without balance impairment; after 5 years of follow-up, age at onset was a significant predictor of the development of balance impairment among patients without balance impairment at baseline, while disease duration was not. In a prevalence study, patients with PD and dementia were significantly older than those without dementia but disease duration was nearly identical. In incidence studies of PD dementia, age but not disease duration was significantly associated with the development of dementia in different cohorts of patients with PD when both variables were examined in the same statistical model. 

The superposition of the effects of the disease process and aging, assuming only additive effects (Figure, panel C), can arguably account for the influence of age on the clinical progression of PD. As indicated by the white line in the Figure (panel C), different structures would reach a degree of neuronal loss at which specific clinical manifestations are expressed at different ages. While neuronal loss in the substantia nigra pars compacta might reach a threshold of clinical expression at an early age, involvement of the nucleus basalis of Meynert contributing to the development of dementia would occur at a more advanced age. Similarly, involvement of the pedunculopontine nucleus reaching a threshold of clinical expression would only occur at a more advanced age. (A role for the pedunculopontine nucleus in the pathophysiology of gait and postural impairment in PD has been suggested by animal and clinical studies.) Alternatively, the superposition of the effects of the disease process and aging may involve an interaction at the level of the underlying causes or mechanisms such that the combined effect of the 2 processes in terms of neuronal loss in relevant structures is greater than the sum of the separate effects.

The observation that the combined effect of 2 variables on an outcome of interest is different from the sum of the separate effects (or, equivalently, that 1 variable modifies the effect of the other) indicates the presence of statistical interaction (or effect modification). In the studies discussed herein, a positive statistical interaction between variables representing the disease process (disease duration or severity of extrapyramidal signs) and aging denotes that the effect of 1 variable on the outcome is greater at higher levels of the other variable. In a cross-sectional clinical investigation assessing motor severity in patients with PD based exclusively on limb bradykinesia, no interaction was observed between the effects of disease duration and age at examination on motor severity. Moreover, in biochemical and positron emission tomography investigations, no interaction was demonstrated between the effects of disease duration and age on the nigrostriatal system degeneration in PD. On the other hand, in a cross-sectional analysis of 451 patients...
with PD with a wide range of disease duration and age, a significant positive interaction was observed between the effects of disease duration and age at evaluation on the severity of bradykinesia (limb plus body), speech impairment, and gait and postural impairment, but not on tremor and rigidity. Consistent with a study including patients with PD and controls that had shown a significant positive interaction between the effects of presence of disease and age group on cognitive impairment, Levy et al reported that the risk of dementia in patients with PD was much higher in those with higher severity of extrapyramidal signs and older age (relative risk, 9.7; 95% confidence interval, 3.9-24.4) than in those with lower severity and older age (relative risk, 1.6; 95% confidence interval, 0.5-4.8) and higher severity and younger age (relative risk, 1.2; 95% confidence interval, 0.5-3.2); all groups were compared with patients with lower severity and younger age (reference group).

These studies suggest the presence of a statistical interaction between variables representing the disease process and aging for non–levodopa-responsive motor and cognitive manifestations of PD, but not for levodopa-responsive manifestations or the underlying nigrostriatal system degeneration. The assessment of statistical interaction is relative to how association is measured (eg, risk ratio as opposed to risk difference). Biologic interaction (“the interdependent operation of 2 or more causes to produce disease”) and statistical interaction (“the interdependence between the effects of 2 or more factors within the confines of a given model of risk”) are not interchangeable concepts. However, biologic interaction can be viewed as the causal or mechanistic counterpart of statistical interaction. Thus, based on the aforementioned evidence, the following can be postulated: The effects of the disease process and aging on nondopaminergic structures involve a biologic interaction. This is schematically represented in the Figure (panel D).

CONCLUSIONS

The proposed model suggests that, within the context of the pathologic process proper to PD, aging may still play a substantive role in PD pathogenesis by way of an interaction with the disease process in nondopaminergic structures. Current descriptions of the pathogenic cascades involved in PD should further account not only for the relative selectivity of the disease process to the substantia nigra pars compacta, but also for the widespread involvement of monoaminergic and cholinergic structures in late clinical stages of the disease. In particular, experiments designed to investigate whether the susceptibility of nondopaminergic structures or cell types to the disease process is synergistically influenced by molecular mechanisms related to the aging process would be relevant to the hypothesis of a biologic interaction between the disease process and aging in nondopaminergic structures. Investigation into this hypothesis might eventually offer opportunities to modify the clinical progression of the disease, because interventions on interacting mechanisms of the disease process and aging would have the potential to delay the emergence of non–levodopa-responsive motor and cognitive manifestations of PD.


**Correction**

Error in Text. In the Original Contribution by Graff-Radford et al titled “Association of Low Plasma Aβ42/Aβ40 Ratios With Increased Imminent Risk for Mild Cognitive Impairment and Alzheimer Disease,” published in the March issue of the Archives (2007;64[3]:354-362), an error occurred in the “Methods” section on page 356. In the subsection titled “Method of Measuring Plasma Aβ40 and Aβ42 Levels,” the fourth sentence should have read as follows: “Plasma Aβ measures were made using an enzyme-linked immunosorbent assay method with the well-characterized antibodies BAN-50/Bα23 specific for Aβ40 and BNT-77/BC03 specific for Aβ42.”