Parkinson Disease With Old-Age Onset

A Comparative Study With Subjects With Middle-Age Onset

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Background: To our knowledge, no prior study has focused on subjects with Parkinson disease (PD) with elderly disease onset, and there is little evidence-based knowledge of treatment outcomes in these patients.

Objective: To compare the clinical presentation, comorbidities, treatment, and evolution of PD in patients with old-age onset with those of patients with middle-age onset in one US university center.

Design: In the Rush Movement Disorder Database, we retrieved 43 patients with PD with onset at 78 years or older. By using a case-control design, we assigned each patient with old-age PD onset 1 (n = 5) or 2 (n = 38) patients with middle-age PD onset, matched for disease duration but with disease onset between the ages of 43 and 66 years. We compared the groups on several clinical measures using conditional logistic regression.

Results: At a comparable length of PD duration (mean, 5.1 years for patients with old-age PD onset and 5.5 years for patients with middle-age PD onset), the total Unified Parkinson's Disease Rating Scale motor score was significantly higher in those with old-age PD onset than in those with middle-age PD onset (33.3 vs 21.2; P < .001). The patients with old-age onset had higher scores for rigidity (5.2 vs 4.3; P = .03), bradykinesia (13.0 vs 9.6; P = .001), and axial impairment (12.8 vs 5.2; P < .001), but not for tremor (2.2 vs 2.0; P = .68). They were more likely to have at least one comorbid condition compared with patients with middle-age onset (24 [56%] of 43 patients vs 20 [25%] of 81 patients; P = .002), but even when adjusting for comorbidities, they still maintained higher motor scores than controls. When treating patients with old-age PD onset, clinicians used levodopa monotherapy more frequently than in patients with middle-age PD onset (34 patients [79%] vs 16 patients [20%]; P < .001), and agonists were prescribed less frequently (5 patients [12%] vs 29 patients [36%]; P = .005).

Conclusions: At the same disease duration, patients with old-age PD onset have greater motor impairment than patients with middle-age PD onset. This difference may be due to more rapid disease progression, less aggressive or less potent medical treatment, the elderly age of the subjects with old-age PD onset at study end independent of disease onset, or yet-to-be elucidated influences of comorbid conditions. Focused research on old-age PD onset is important to delineate the confounding influences of aging and comorbidities and to establish the safety and efficacy of new treatments for this group of patients.

Arch Neurol. 2003;60:529-533
3 studies have specifically analyzed clinical impairment in patients with PD onset after the age of 70 years. The results of these studies disagree concerning the outcome over time. To our knowledge, no prior study has focused on subjects with old-age PD onset. There is also little evidence-based knowledge of treatment outcomes in these very old patients, because they are generally excluded from clinical trials. Even observational retrospective therapeutic studies are unusual in this age group.

Because elderly patients represent a growing population of subjects with PD and little is known about the prognosis and adequate therapeutic management for these elderly patients, we conducted this study on patients with old-age PD onset. We used a case-control method and analyzed clinical signs, comorbidities potentially aggravating the parkinsonian symptoms, treatment regimens, and dosages in subjects with PD onset at 78 years or older compared with subjects with PD onset between the ages of 43 and 66 years. We hypothesized that patients with old-age PD onset would have a milder disease course, comparable to cancer progression at this age, but that comorbidities would be more frequent. Finally, we expected less aggressive PD treatment in these patients.

METHODS
PATIENTS

We consulted the Rush Movement Disorder Database, covering January 1, 1995, to June 30, 2000, containing visit information for 2389 patients with idiopathic PD. In July 2000, we retrieved 43 patients with disease onset at 78 years or older, at least one follow-up examination, and a complete Unified Parkinson's Disease Rating Scale (UPDRS) examination at their last visit. The diagnosis of PD was based on the assessment of 1 of 6 experienced movement disorder specialists. Cases considered by the treating physician as atypical parkinsonism, vascular parkinsonism, or any PD plus syndrome were excluded. By using a case-control design, each patient with old-age PD onset was matched with 2 (n=38) or 1 (n=5) control patient with PD onset between the ages of 43 and 66 years, and of same sex and same disease duration (±2 years). The cutoff ages for the patients 78 years or older, called patients with old-age PD onset, and for the control patients between the ages of 43 and 66 years, called patients with middle-age PD onset, were empirically defined, based on the available study subjects in the database and with the goal to have (1) groups of sufficient size for proper statistical analysis and (2) the largest possible age gap between groups. For patients with old-age PD onset, their last medical visit before July 2000 was defined as their target date, and disease duration, calculated to this point, served to determine a comparable examination target date for the patients with middle-age PD onset. The medical record review and standardized database consultation gathered the following data, available at the target visit: UPDRS motor score; comorbidities, as noted in the medical record by the clinician during the last visits; PD medication; and other medications. When calculating the total medication dosages, we used the following equivalencies: (1) 1 mg of slow-released levodopa equals 0.7 mg of regular levodopa; and (2) dopamine agonists are expressed in pergolide equivalents, with 1 mg of pergolide equal to 10 mg of bromocriptine, equal to 1 mg of pramipexole, equal to 3 mg of ropinirole. The study was approved by the Institutional Review Board of Rush-Presbyterian-St Luke's Medical Center.

RESULTS

PATIENT CHARACTERISTICS

The average onset age was 82.2 years (SD, 3.4 years; range, 78-92 years) for the patients with old-age PD onset and 54.7 years (SD, 4.1 years; range, 43-66 years) for the patients with middle-age PD onset. The average duration of PD at the last visit was 5.1 (SD, 2.6) years for patients with old-age onset and 5.5 (SD, 2.6) years for patients with middle-age onset (P=.46). Nineteen (44%) of the patients with old-age onset and 37 (46%) of the patients with middle-age onset were men.

At the target date, the UPDRS motor score was significantly higher in patients with old-age onset than in patients with middle-age PD onset. Patients with old-age PD onset had significantly higher rigidity, bradykinesia, and axial impairment scores than patients with middle-age PD onset. However, patients with middle- and old-age onset did not differ in tremor ratings (Table 1).

COMORBIDITIES

Patients with old-age PD onset were more likely to have comorbid conditions than patients with middle-age PD onset. Specific comorbidities more common in patients with old-age onset than in patients with middle-age onset were cerebrovascular disease, auditory deficits (especially presbycusis), and visual impairment (cataract, glaucoma, and macular degeneration) (Table 2). Neither osteoporosis nor arthritis was documented significantly more often in patients with old-age onset than in patients with middle-age onset. Dementia was documented in 6 patients with old-age PD onset (14%) and in 1 patient with middle-age PD onset (1%). These low crude numbers precluded statistical comparison. When adjusting for any comorbidities as potentially interfering variables, patients with old-age onset still had higher motor scores than patients with middle-age onset (Table 3).

STATISTICAL ANALYSIS

The statistical analysis used descriptive statistics and conditional logistic regression. Means and SDs are presented for continuous variables (age, duration of PD, and subscales of the UPDRS motor score), and proportions are calculated when investigating categorical variables (comorbidities and drugs). All significance testing comparing patients with old-age PD onset with patients with middle-age PD onset was performed using conditional logistic regression (a logistic model that takes the matching into account), unless small numbers (counts of 0 or 1 after cross tabulations) prevented doing so. Additional exploratory models were performed, adjusting for comorbidities. The results are presented using relative risks and 95% confidence intervals. A relative risk of greater than 1 corresponds to a higher score for cases compared with controls. A 95% confidence interval that does not contain 1 signals a statistically significant difference between scores in cases and controls after adjusting for comorbidities. In such instances, an exact inference was made, using the binomial distribution and taking into account the matched design. All performed tests were 2-sided, with α = .05.
onset (defined as onset at young PD onset (defined as onset at 40 years) vs old age PD onset differed in exposure to medications that could aggravate PD, we compared use of the following drug classes: calcium antagonists, dopamine receptor blockers, and antihypertensive agents. Exposure to one, all, or any combination of these classes was not more frequent among the patients with old-age onset than the patients with middle-age PD onset.

To evaluate whether patients with old- and middle-age PD onset differed in exposure to medications that could aggravate PD, we compared use of the following drug classes: calcium antagonists, dopamine receptor blockers, and antihypertensive agents. Exposure to one, all, or any combination of these classes was not more frequent among the patients with old-age onset than the patients with middle-age PD onset.

Table 1. Comparison of UPDRS Subscale Scores Between Cases and Controls

<table>
<thead>
<tr>
<th>UPDRS Subscale at the Target Date†</th>
<th>Cases (n = 43)</th>
<th>Controls (n = 81)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor (0-92) [item 19]</td>
<td>33.3 ± 12.2</td>
<td>21.2 ± 10.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tremor (0-16) [item 20]</td>
<td>2.2 ± 2.8</td>
<td>2.0 ± 2.1</td>
<td>.68</td>
</tr>
<tr>
<td>Rigidity (0-20) [item 22]</td>
<td>5.2 ± 2.2</td>
<td>4.3 ± 2.2</td>
<td>.03</td>
</tr>
<tr>
<td>Bradykinesia (0-32) [item 23]</td>
<td>13.0 ± 5.8</td>
<td>9.6 ± 5.0</td>
<td>.001</td>
</tr>
<tr>
<td>Axial impairment (0-28) [item 27]</td>
<td>12.8 ± 6.1</td>
<td>5.2 ± 3.8</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: LLE, left lower extremity; LUE, left upper extremity; RLE, right lower extremity; RUE, right upper extremity; UPDRS, Unified Parkinson’s Disease Rating Scale.

Comment

At the same disease duration of approximately 5 years, patients with old-age PD onset had greater motor impairment, as rated by the UPDRS, than subjects with middle-age PD onset. This observation strictly refutes our original hypothesis of a milder disease course when there is very late disease onset. The difference was evident for axial impairment signs, including gait and posture, and it also affected bradykinesia and rigidity. Only tremor severity was not different in the 2 groups. Similar findings have been observed in comparisons of patients with young PD onset (defined as onset at <40 years) vs old onset (defined as onset at >60 or >70 years). Together, these data establish that, with increasing age of PD onset, axial and hypokinetic parkinsonian symptoms become more severe and may even predominate the clinical presentation. Our study extends these observations to patients with disease onset in their late 70s and 80s, and uses a robust case-control method with a large mean
interval of age of onset (28 years) between those with middle-age and those with old-age onset.

The distinctive phenotype of PD with old-age onset may relate to different reasons: first, a different natural course of parkinsonism may occur among older persons because of an implicitly different extent or rate of nigrostriatal degeneration in very elderly persons; second, reduced compensatory mechanisms may exist in the very old brain, leading to a quantitatively more pronounced impairment with more rapid disease progression; and third, there may be higher motor impairment because of the more frequent comorbidities. Comorbidities in those with PD have not been investigated so far in living patients, but have been analyzed in one study using data from death certificates. The 2 studies support one another in documenting many cerebrovascular diseases in patients with old-age PD onset. A detection bias cannot be excluded, however, for both studies because neurologists may be more apt to diagnose and document comorbidities in elderly patients. Our method did not permit a clear delineation of the causative role of vascular disease relative to the primary neurodegeneration in these subjects, all of whom were diagnosed by clinical movement disorder specialists as having typical PD and not vascular parkinsonism. In contrast to vascular comorbidities, arthritis and osteoporosis were surprisingly low among patients with old-age PD onset. Although we cannot exclude underreporting of these common signs associated with senescence, the data suggest that nonspecific comorbidities affecting dexterity and mobility do not adequately explain the higher motor impairment scores on the UPDRS among patients with old-age PD onset. We specifically corrected our analysis to adjust for comorbidities and still found continued significant differences in UPDRS scores.

As hypothesized, less aggressive treatment strategies were used in patients with old-age PD onset. The clinicians preferred monotherapy with levodopa vs a combination with dopamine agonists or the use of agonists alone. The mean dosages of all drugs were similar in both age groups. We recognize that these treatment strategies reflect only one center’s approach, but we suggest that they reflect a more generalized reluctance to use complex treatment combinations in the patients with old-age onset. One recent report argued for the safety of dopamine agonists in the elderly population. However, the actual efficacy and safety of various monotherapies and combination therapies are unknown, because very elderly patients are generally excluded from random prospective studies or, if included, are not presented as a separate subgroup. Patient sensitivity to treatment may change with age, and a less robust clinical effect of the immediate levodopa test has been shown in elderly patients with PD.

Another potential influence on prescribing patterns could also relate to cognitive deficits among elderly patients. Valid data on cognitive impairment and psychiatric symptoms are missing from our report because they were not systematically recorded for all subjects. Consequently, we cannot exclude that such problems, real or expected, influenced the clinicians’ choice for less aggressive treatment in the patients with old-age onset. On the other hand, it is also possible that patients with old-age onset, without psychiatric symptoms or dementia, who attended a tertiary care center staffed by PD specialists may request assertive, albeit careful, treatment precisely because these physicians are experienced in the field. Others have found that predominant axial impairment can be associated with incident dementia.

In this study, we did not systematically monitor the presence and severity of adverse effects of antiparkinsonian drug treatment. The most important adverse effects in the literature are dyskinesias and psychotic signs. Dyskinesias, especially of the dystonic and ballistic types, have frequently been reported in patients with young-onset PD. One researcher report that psychotic adverse effects predominate in the elderly patients with PD. Our study design was not longitudinal, and we documented only cross-sectional data on PD signs and treatment. A prospective study with systematic data collection at several times would permit an analysis of the evolution of disability and impairment. However, when designing the present study, we realized that patients with old-age PD onset were not seen as regularly and frequently as patients with middle-age PD onset. We cannot exclude a preselection toward benign cases of parkinsonism among the very old, because the study assessments took place at a tertiary referral center to which patients had to travel. Those patients who travel to a tertiary care center may tend to have fewer comorbidities than those patients with PD remaining in the community for health care. The medical records do not always document educational level or economic standing. Finally, the lack of brain imaging precludes the exclusion of anatomically visible confounding variables, such as diffuse or focal brain atrophy or lacunar infarcts in strategic regions for motricity. Some specific hyperintensities on magnetic resonance imaging scans have been useful for the differentiation of nonparkinsonian gait disturbances in elderly patients: frontal periventricular hyperintensities are sensitive, and parieto-occipital periventricular hyperintensities are specific.

A final explanation for the observed differences could relate to the old age of the old-age onset cohort, independent of onset age. It is possible that, regardless of onset age, when PD is superimposed on the very old brain, the outcome is clinically more severe than the impairment seen in middle-aged subjects. To test this hypothesis, we would need control groups composed of old subjects matched for age at the time of data collection but with middle-age onsets. We are in the process of identifying this cohort. While some of these limitations are likely to persist in future studies of this select population, we consider the very elderly population with PD an important focus for research and clinical trials. We encourage further studies analyzing the impact of frequent comorbidities on the clinical expression of PD and randomized clinical trials to delineate the therapeutic responses of these patients in terms of safety and efficacy and to investigate different dosing schedules.

Accepted for publication December 2, 2002.

Author contributions: Study concept and design (Drs Diederich and Goetz); acquisition of data (Dr Diederich and Ms Chmura); analysis and interpretation of data (Drs...
REFERENCES


