Subjective Complaints Precede Parkinson Disease

The Rotterdam Study

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Background: Neuronal degeneration and dopamine loss in the preclinical phase of Parkinson disease may produce subtle complaints before clinically recognizable symptoms emerge.

Objective: To examine whether subjective complaints of stiffness, slowness, tremors, or postural imbalance in persons without clinical signs of parkinsonism are related to an increased risk of future Parkinson disease.

Design: Population-based cohort study. We recorded subjective complaints of stiffness, slowness of movement, tremors, falling, or a feeling of imbalance in a standardized interview of 6038 participants without dementia in whom no parkinsonian signs were found on physical examination at baseline, and we studied them prospectively for the occurrence of incident Parkinson disease.

Setting: General population.

Participants: A total of 6038 participants who were free of dementia and parkinsonian signs.

Main Outcome Measures: Incident Parkinson disease. Participants were examined in person both at baseline (January 1990–June 1993) and at 2 follow-up visits (September 1993–December 1994 and April 1997–December 1999), and the cohort was continuously monitored through computerized linkage of the study database to general practitioners' medical records. We analyzed the data using Cox proportional hazards regression models.

Results: Participants who reported stiffness, tremors, or imbalance at baseline had a significantly increased risk of developing Parkinson disease during follow-up (for stiffness, hazard ratio, 2.11; 95% confidence interval, 1.25-3.55; \( P = .005 \); for tremors, hazard ratio, 2.09; 95% confidence interval, 1.12-3.90; \( P = .002 \); and for imbalance, hazard ratio, 3.47; 95% confidence interval, 1.69-7.00; \( P = .001 \)).

Conclusions: Subjective complaints of stiffness, tremors, and imbalance are associated with an increased risk of future Parkinson disease and may reflect early effects of dopamine shortage, even when standard neurological testing cannot yet demonstrate any motor symptoms.

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METHODS

ROTTERDAM STUDY

The Rotterdam study is a prospective population-based cohort study of determinants of diseases in elderly persons. Of all inhabitants aged 55 years and older of a district of Rotterdam, the Netherlands, 7983 subjects (response rate, 77.7%) agreed to participate. Both at baseline (January 1990–June 1993) and in 2 follow-up rounds (September 1993–December 1994 and April 1997–December 1999), all of the participants were interviewed and underwent extensive physical examination, including cognitive screening and screening for parkinsonian signs. In addition, the cohort was continuously monitored for major disease outcomes and mortality through computerized linkage to general practitioners' medical records. Informed consent was obtained from each participant, and the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, approved the study.
SUBJECTIVE COMPLAINTS ASSESSED DURING THE BASELINE INTERVIEW

At baseline, all of the participants were interviewed at their homes by means of a standardized questionnaire. This questionnaire included a set of 5 symptom-specific questions that concerned the 4 cardinal signs that are characteristic of PD. Participants were asked to indicate whether they ever experienced stiffness (rigidity), tremors of the head, arms, or legs (resting tremor), slowness of movement (bradykinesia), falling, or a feeling of imbalance (with falling and feeling of imbalance both related to postural imbalance). We assessed imbalance in a stepwise fashion by asking participants whether they ever experienced dizziness, and if so, to specify whether this concerned a near-fainting sensation (presyncope), spinning sensation (vertigo), feeling of imbalance (disequilibrium), or the perception of lacking control over leg movement.

ASSESSMENT OF PD

At both baseline and follow-up, we used a 2-phase design to identify subjects with PD.12,13 All of the participants were screened for parkinsonian signs (rigidity, resting tremor, bradykinesia, and impaired postural reflexes) in a standardized way. Individuals who screened positive received a structural diagnostic workup comprising the Unified Parkinson Disease Rating Scale14 and neurological examination. Additional information obtained from the computerized surveillance system was reviewed by a panel of neurologists and research physicians. A neurologist examined persons who were suspected of having PD to confirm the diagnosis. Parkinsonism was diagnosed if at least 2 parkinsonian signs were present in a subject not receiving antiparkinsonian drugs or if at least 1 sign had improved after the subject began receiving medication. Parkinson disease was diagnosed when all of the causes of secondary parkinsonism (parkinsonism due to dementia, use of neuroleptics, cerebrovascular disease, multiple system atrophy, or progressive supranuclear palsy) could be excluded.

STUDY POPULATION

At baseline, 6818 participants underwent neurological screening and provided information on subjective complaints. Of those participants, 116 were diagnosed with any parkinsonism, including 89 PD cases.12 To examine the relationship between baseline subjective complaints and the risk of incident PD, we excluded all of the participants diagnosed with any parkinsonism or dementia at baseline, as they could no longer fulfill the criteria for incident PD.12 Because absence of parkinsonism does not preclude the presence of 1 cardinal sign and to be maximally sure to evaluate subjects free of any parkinsonism, we only studied participants in whom none of the parkinsonian signs were found during the baseline neurological screening. This resulted in a study population at risk for PD of 6038 persons free of parkinsonian signs and dementia at baseline.

DATA ANALYSIS

Because the complaints that we studied specifically concerned the cardinal signs of PD, we first evaluated whether they were cross-sectionally related to the presence of PD at baseline. Odds ratios for PD according to the presence of each complaint were calculated through binary logistic regression and were adjusted for age and sex. To examine the association between baseline complaints in participants without dementia who were free of parkinsonian signs and the risk of future PD, we used Cox proportional hazards regression analysis to calculate hazard ratios adjusted for age and sex.

RESULTS

Baseline characteristics of the study population are shown in Table 1. The prevalence of self-reported complaints suggestive for parkinsonism appears considerably high in the elderly population, even in persons without any parkinsonian signs on physical examination. More than half of the participants (52.1%) reported at least 1 of the 5 complaints related to the typical features of PD. Stiffness was reported by almost one third of the study population, slowness by one fifth, and tremors, imbalance, and falling each by over 10% (Table 1). Results of the cross-sectional analysis are shown in Table 2. The vast majority (92.1%) of individuals diagnosed with PD at baseline had at least 1 complaint, and 75.3% reported at least 2 complaints. As expected, reported stiffness, falling, and especially slowness of movement and tremors were strongly related to the presence of PD at baseline.
In this population-based study, a considerable proportion of the elderly participants experienced stiffness, slowness, tremors, falling, or a feeling of imbalance. Even among persons without any parkinsonian signs on clinical examination, more than half of the participants reported at least 1 of these complaints. Furthermore, persons who reported stiffness, tremors, or a feeling of imbalance at baseline had an increased risk of developing PD during follow-up. One of the major strengths of this study is its prospective design; complaints were assessed while future disease status was unknown, and therefore, recall bias is not an issue. Moreover, we used in-person screening of participants instead of register-based methods to assess parkinsonism. This limits the possibility that at baseline, participants with relatively early or mild PD who had not yet sought medical attention were incorrectly diagnosed as not having PD. We restricted our study population to those participants in whom no abnormalities were found on physical examination specifically aimed at detecting parkinsonian signs. We also believe that incorrect diagnoses during follow-up were unlikely. Follow-up was almost complete, we applied strict diagnostic criteria for PD, and we continued to follow up participants after a diagnosis had been made, which enabled us to revise diagnoses on the basis of additional information if necessary. Unfortunately, we could not perform in-person reexaminations of all of the participants owing to death, refusal, or inability to visit the research center because of disease or handicaps. One might thus argue that incident PD cases may have been missed, probably especially those with the postural instability gait disorder–dominant form of PD, which is more difficult to diagnose without standardized screening. However, since the majority of participants underwent direct examination and the computerized surveillance system provided virtually complete coverage for those who could not be seen, we think this possibility is limited and will not have affected our results substantially. Limitations of the baseline questionnaire include absence of questions on the duration of reported symptoms but may result in subtle signs that are very mild or only intermittently present and therefore not entirely asymptomatic. Subjective complaints related to motor function might indicate a very early phase of not-yet-diagnosable PD during which dopamine loss is not sufficient to produce overt typical PD symptoms but may result in subtle signs that are very mild or only intermittently present and therefore not likely to be detected in routine screening or examination. In our study, falling was related cross-sectionally but not prospectively to the risk of PD whereas the opposite held true for a subjective feeling of imbalance. Perceived imbalance may be a very early symptom that progresses to overt postural instability and an increased risk of falling later in the course of the disease. In the same way, a subjective feeling of stiffness may precede clinically detectable rigidity, and patients may experience occasional tremors long before clinical examination confirms their perception.

It has been observed that prior to developing clinically manifest PD, many patients experience a range of nonspecific symptoms, such as depression, fatigue, anxiety, or pain.8,9

### Table 3. Subjective Complaints Related to Motor Function and the Risk of Incident Parkinson Disease

<table>
<thead>
<tr>
<th>Complaint</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiffness</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes†</td>
<td>2.11 (1.25-3.55)</td>
</tr>
<tr>
<td>No†</td>
<td>1.00</td>
</tr>
<tr>
<td>Tremor of arms, legs, or head</td>
<td>2.09 (1.12-3.90)</td>
</tr>
<tr>
<td>No†</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes†</td>
<td>1.49 (0.84-2.65)</td>
</tr>
<tr>
<td>Slowness of movement</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes†</td>
<td>3.47 (1.69-7.00)</td>
</tr>
<tr>
<td>Feeling of imbalance</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes†</td>
<td>0.61 (0.27-1.36)</td>
</tr>
<tr>
<td>Falling</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio. *Hazard ratios with 95% CIs were adjusted for age and sex. †Reference variables.
Similar findings have been observed in prospective studies of Alzheimer disease or cerebral small vessel disease that showed that subjective memory complaints in persons without objective cognitive impairment were associated with an increased risk of developing dementia or more white matter lesions. Both PD and Alzheimer disease are characterized by a phase of neuronal degeneration and loss of function before the appearance of typical symptoms, and apparently, such a preclinical phase also exists in slowly progressive vascular disease. Researchers have shown particular interest in possible markers of preclinical disease since putative neuroprotective agents would ideally be administered as early as possible in the degenerative process and preferably before clinical symptoms appear.

Several potential biomarkers for presymptomatic PD are now being investigated, such as the loss of the dopamine transporter detected by positron emission tomographic imaging, subtle abnormalities on psychological testing, olfactory dysfunction, and biochemical markers in serum or cerebrospinal fluid. A questionnaire on complaints related to motor function is in itself probably of limited use as a preclinical marker. In spite of the strong associations between self-reported complaints and the risk of future PD, the specificity will be low given the high proportion of elderly persons reporting these complaints. Combined with the relatively low prevalence and incidence of PD in the general population, this will result in a low positive predictive value (defined as the proportion of persons with a positive test who will actually develop the disease). As a matter of fact, in our data, each of the subjective complaints had a positive predictive value of no higher than 1.0% to 2.5%, which is clearly insufficient for a questionnaire to be used alone as a marker for preclinical disease. It is, however, generally believed that a single test will unlikely fulfill all of the criteria for the ideal biomarker and that, presumably, a stepwise approach with a simple and inexpensive initial screening test is required. A questionnaire on subjective complaints might qualify for being part of such a first step.

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REFERENCES