ORIGINAL CONTRIBUTION

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.

Arch Neurol. 2006;63:362-365

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PARKINSON DISEASE (PD) IS caused by a selective degeneration of the dopaminergic neurons in the substantia nigra of the brain.[1] The typical clinical signs of PD (tremor, rigidity, bradykinesia, and postural instability) begin to appear when degeneration and associated dopamine loss exceed 50%.[2,3] Manifest PD is thus preceded by a preclinical phase of several years during which neuronal degeneration develops without motor symptoms being present yet.[4] Evidence suggests, however, that nonmotor abnormalities may occur during this phase, such as olfactory dysfunction, personality disturbances, and depression.[3,5-8] More general nonspecific symptoms have also been described to predate the typical PD signs for several years.[9] We hypothesized that moderate dopamine deficiency in preclinical PD might result in subtle subjective complaints specifically related to motor function, and we examined whether these complaints were associated with an increased risk of PD in the future in a prospective population-based cohort study.

METHODS

ROTTERDAM STUDY

The Rotterdam study is a prospective population-based cohort study of determinants of diseases in elderly persons.[10] 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.[11-13] In addition, the cohort was continuously monitored for major disease outcomes and mortality through computerized linkage to general practitioners' medical files. Informed consent was obtained from each participant, and the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, approved the study.

Table 1. Baseline Characteristics of the Study Population (n = 6038)

Characteristic	Value*
Age, mean (SD), y	68.5 (8.5)
Women	3569 (59.1)
Subjective complaints	
Stiffness	1938 (32.1)
Tremor of arms, legs, or head	636 (10.5)
Slowness of movement	1262 (20.9)
Feeling of imbalance†	524 (10.7)
Falling	905 (15.0)
≥1 Complaint	3146 (52.1)
≥2 Complaints	1359 (22.5)

*Values are expressed as number (percentage) unless stated otherwise.
†Feeling of imbalance was assessed in 4897 participants.

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 Scale[14] 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.

Table 2. Association Between Reported Complaints and the Presence of Parkinson Disease Cross-sectionally at Baseline

Complaint	OR (95% CI)*
Stiffness	
No†	1.00
Yes	2.43 (1.58-3.73)
Tremor of arms, legs, or head	
No†	1.00
Yes	13.61 (8.45-21.92)
Slowness of movement	
No†	1.00
Yes	5.97 (3.74-9.52)
Feeling of imbalance	
No†	1.00
Yes	1.27 (0.62-2.61)
Falling	
No†	1.00
Yes	2.60 (1.66-4.08)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Odds ratios with 95% CIs were adjusted for age and sex.
†Reference variables.

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.

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

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

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Hazard ratios with 95% CIs were adjusted for age and sex.
†Reference variables.

Table 3 shows the relationship between reported complaints at baseline and the risk of developing PD during follow-up in participants without dementia who screened negative for any parkinsonian signs on routine examination. Follow-up information was available for 98.8% of the participants, either through in-person reexamination or the continuous surveillance system. Complete in-person reexamination was performed in 80.6% of the participants (84.6% of those still alive) in the first follow-up round and in 62.4% (74.4% of those still alive) in the second follow-up round. During a total of 35 429 person-years of follow-up (mean follow-up, 5.8 years), 56 new cases of PD were identified. Of those, 43 cases were detected through the structured workup at the research center and 13 through the computerized surveillance system. Mean (SD) follow-up after disease onset of the incident cases was 4.3 (1.8) years.[11] Of the participants who developed PD during follow-up, 71.8% had reported at least 1 complaint and 41.0% reported at least 2 complaints related to motor function at baseline. Complaints of stiffness at baseline were significantly associated with more than a 2-fold increased risk of future PD (hazard ratio, 2.11; 95% confidence interval, 1.25-3.55; $P=.005$), as were reported tremors of arms, legs, or head (hazard ratio, 2.09; 95% confidence interval, 1.12-3.90; $P=.002$). Interestingly, self-reported falling and slowness of movement, which were both significantly cross-sectionally related to the presence of PD at baseline (both $P<.001$), were not prospectively associated with an increased risk of future PD ($P=.23$ and $P=.18$, respectively). A feeling of imbalance, on the other hand, showed a strong association with a future diagnosis of PD (hazard ratio, 3.47; 95% confidence interval, 1.69-7.00; $P=.001$) but no significant association with the presence of PD at baseline ($P=.52$).

COMMENT

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.[12] 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 complaints, which precludes potentially interesting subanalyses, and the fact that both limb and head tremor were assessed in 1 question. Because head tremor usually is not considered typical for PD, a question about limb tremor only would probably have yielded more PD-specific results.

Our findings support the notion that clinically manifest PD is preceded by a preclinical phase that is 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]

Similar findings have been observed in prospective studies[15-18] 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,[4] 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.[19,20] Several potential biomarkers for presymptomatic PD are now being investigated, such as 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.[5,20,21] 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,[12,22] 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.[4,20] A questionnaire on subjective complaints might qualify for being part of such a first step.

Published Online: January 9, 2006 (doi:10.1001/archneur.63.3.noc50312).
Accepted for Publication: November 4, 2005.
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Author Contributions: *Study concept and design:* de Lau and Breteler. *Acquisition of data:* de Lau, Koudstaal, and Breteler. *Drafting of the manuscript:* de Lau and Breteler. *Critical revision of the manuscript for important intellectual content*: de Lau, Koudstaal, Hofman, and Breteler. *Statistical analysis:* de Lau and Breteler. *Obtained funding:* Hofman and Breteler. *Study supervision:* Breteler.
Funding/Support: This study was supported by grant 015.000.083 from the Netherlands Organization for Scientific Research, The Hague. The Rotterdam Study is supported by the Erasmus Medical Center and Erasmus University, Rotterdam, the Netherlands; the Netherlands Organization for Scientific Research, the Netherlands Organization for Health Research and Development, the Research Institute for Diseases in the Elderly, the Ministry of Education, Culture, and Science, and the Ministry of Health, Welfare, and Sports, The Hague; the European Commission (DG XII), Brussels, Belgium; and the municipality of Rotterdam.
Role of the Sponsor: The sponsors of the study had no role in study design, data collection, data analysis, or writing of the report.
Acknowledgment: The contributions of the general practitioners and pharmacists of the Ommoord district to the Rotterdam Study are gratefully acknowledged.

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