

Reliability of Reported Age at Onset for Parkinson's Disease

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Abstract: An individual's age at onset of Parkinson disease (PD) can be collected through a variety of sources, including medical records, family report, and clinical observation. The most common source of PD age at onset information in the research setting is family-report, which is then typically used to classify a subject as juvenile, young, or late age at onset. The reliability of the family-reported age at onset of PD has not been rigorously examined. The present study used data from individuals diagnosed with PD to evaluate the reliability of age at onset information by comparing data obtained from three sources: 1) the subject's medical

records, 2) a Family History Questionnaire, and 3) a Subject History Questionnaire. Among the 149 subjects with data for all three age at onset sources, the estimated reliability was $R = 0.94$. Similar reliability was observed when the sample was stratified based on gender, age at examination, disease duration, first symptom of PD, and years of education. The three measures of age at onset of PD show excellent agreement, strengthening confidence in the reliability of the reported age of clinical onset for PD. © 2002 Movement Disorder Society

Key words: Parkinson's disease onset; test-retest reliability

Studies designed to better understand the etiology of Parkinson disease (PD) have often used age at onset of the initial symptoms of disease as one of the means to categorize or classify subjects with PD. This approach has led to the classification of subjects as juvenile (onset < 20 years of age), young-onset (onset 21–40 years of age), and late-onset (onset > 40 years of age) PD.^{1,2} This classification played a role in the identification of two genes resulting in juvenile onset (*parkin*)³ and adult onset (*α-synuclein*)⁴ PD. Studies have localized at least five additional genes contributing to disease susceptibility.^{5–9}

In the absence of prospective information, retrospectively reported age at onset of PD has been used for determining when the clinical symptoms of the disease

first appeared. Unfortunately, unreliable age at onset data may confound, mask, or alter our understanding of the nosology and etiology of PD. To date, the reliability of reported age at onset of PD as captured from various sources has not been investigated. The objective of this study was to measure the reliability of reported age of clinical onset of PD among different sources: medical records, a self-administered questionnaire completed at home by the patient or a family member, and a survey instrument completed during a face-to-face interview by a medical professional based on responses given by the subject or a family member.

PATIENTS AND METHODS

The sample consisted of sibling pairs concordant for PD who were participants in a multicenter genetic linkage study conducted in North America (the United States, Canada, and Puerto Rico). Subjects were evaluated by movement disorder specialists who were members of the Parkinson Study Group (PSG). Sibling pairs, both of whom were either diagnosed with PD or suspected to have PD, were recruited through the PSG sites and also through a variety of other media, including written liter-

†See Appendix for a list of Study participants.

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ature and the Internet. A Family History Questionnaire (FHQ) was mailed to each study participant and completed by either the affected individual or a close family member, typically the spouse or child of the affected individual. The FHQ included an item requesting the age at initial symptom onset of PD. This question was "Age you suspect the source person began showing symptoms of PD."

All relevant medical records were obtained and reviewed to identify the subject's medical diagnosis and the age at onset of PD. Medical records were typically obtained from all physicians who might have diagnosed or evaluated the patient, including movement disorder specialists, neurologists, or family physicians. When available, medical records were obtained from multiple sources.

If the subject and their sibling satisfied initial study eligibility criteria, a study visit was scheduled. During the study visit, a Subject History Questionnaire (SHQ), which has demonstrated substantial test-retest reliability ($\kappa = 0.93$)¹⁰, was administered to each study participant. This questionnaire was administered orally, and the information was obtained from the subject or, if necessary, the accompanying family member, particularly if the patient appeared to have possible cognitive impairment or was a poor historian. Answers to specific questions allowed the collection of data on age at onset of PD, age at diagnosis of PD, and first PD symptom. These questions were "Date PD symptoms were first noted by the subject" and "Date of PD diagnosis." The source of the information provided on the SHQ was noted as belonging to one of the following three categories: "self," "spouse," or "other."

Additionally, for a final determination of PD diagnosis, a PSG movement disorder specialist examined the subjects. All participants completed a uniform clinical evaluation that consisted of Parts II and III of the Unified Parkinson Disease Rating Scale (UPDRS)¹¹ and the Hoehn and Yahr Severity Score.¹² A diagnostic checklist was developed based on the results of clinicopathological studies of parkinsonism so as to reach an acceptable degree of diagnostic specificity and sensitivity.^{13,14} All study participants were then classified as either verified PD (VPD) or nonverified PD (NVPD), based on the results of the diagnostic checklist. Only those subjects who were classified as VPD were included in this analysis. To assess cognitive status, each subject also completed the Mini-Mental State Examination (MMSE)¹⁵ during the face-to-face interview conducted as part of the study visit.

Disease duration (in years) was computed for each subject on the basis of the time that had elapsed from the initial symptom onset, as reported in the medical records, until the subject's Study Visit. Each participant was

classified into one of three groups based on their age at the time of participation (0–64, 65–74, and ≥ 75). The reliability of the three reports of age at onset was calculated, using the intraclass correlation coefficient.¹⁶ The effects of gender, age at study visit, duration of disease, first symptom, and years of education were tested by recomputing the intraclass correlation coefficient (ICC) for each of these subsets. Significant effects were determined by performing a chi square test for heterogeneity.¹⁷

RESULTS

The final sample included 149 individuals who met criteria for a final diagnosis of verified PD and had information regarding the age at onset from all three sources: medical records, FHQ, and SHQ. The demographic properties of the sample studied are listed in Table 1. The majority of study participants (64.4%) had an MMSE score greater than or equal to 28. On the SHQ, the individual providing the information was indicated. In this study sample, 78% of the individuals responded to form questions themselves. For the remaining participants, either the spouse provided the information (7%) or another individual (15%), often a child or caregiver attending the study visit, responded to the questions regarding age at onset and age at clinical diagnosis.

The average age of PD onset from each of the three sources is presented in Table 2. Pair-wise comparison of each source of age at onset information only identified one comparison in which the age at onset information was significantly different. The age at onset reported on the medical records was significantly older than that reported on the SHQ ($P = 0.002$), although the reported age at onset between the two sources differed by less than 1 year.

Among these subjects, the estimated reliability of the age at onset information was $R = 0.94$. To evaluate the effect of gender, age at exam, disease duration, first symptom of PD, and education, the intraclass correlation

TABLE 1. Sample demographics

Variable	Mean \pm SD	Range
Age at time of exam (yr)	68.2 \pm 9.2	36–87
Disease duration	8.5 \pm 7.2	0–34
Hoehn and Yahr	2.5 \pm 0.9	1–5
Education (yr)	13.9 \pm 3.7	6–27
Mini-Mental State Examination	26.9 \pm 4.7	2–30
Gender (male)	89 (59.7%)	
Race (Caucasian)	142 (95.3%)	
First symptom (tremor)	78 (52.7%)	
First symptom (bradykinesia)	15 (10.1%)	
First symptom (loss of energy/fatigue)	8 (5.4%)	
First symptom (change in writing)	7 (4.7%)	
First symptom (poor balance)	6 (4.1%)	

TABLE 2. Average age at onset and duration of disease as reported on three source instruments

	Medical records	FHQ	SHQ
Average age at onset (yr)	59.7 ± 10.8 (range, 27–81)	59.2 ± 11.3 (range, 25–83)	58.9 ± 11.7 (range, 17–82)
Average duration (yr)	8.5 ± 7.2 (range, 0–34)	9.0 ± 8.1 (range, 0–43)	9.3 ± 8.1 (range, 1–35)

FHQ, Family History Questionnaire; SHQ, Subject History Questionnaire.

coefficient was calculated for subsets of the data stratified for these variables (Table 3). There was little difference in the estimated reliability of the data when the sample was stratified on gender, initial symptom of PD, or years of education. The other variables that reduced the reliability score among the instruments were age at exam, with the youngest group having lower reliability among the data sources ($R = 0.84$; $P = 0.11$) and the duration of disease, with those reporting a clinical duration of PD from 5 to 9 years having lower reliability among the data sources ($R = 0.78$; $P < 0.0001$).

DISCUSSION

Data on the age at onset of the first clinical symptom of PD is subjective, taking into account the insidious nature of PD and the ability of individuals to recognize its clinical manifestations. Nevertheless, researchers have used age at onset of PD as a means to classify patients. The importance of age at onset data has increased with the report of greater familiarity of PD in families with earlier age at onset.¹⁸ Although we have identified nominally significant differences in age at onset between the medical record information and the self-report data, the

actual difference, on average, between these sources is less than 1 year. Thus, although because of our relatively large sample size ($n = 149$) we detected a significant difference in the age at onset information provided through two sources, the clinical relevance of this difference is quite minor, i.e., the actual difference in reported age at onset was less than 1 year. Our results demonstrate that data on self- or family-reported age at onset of PD is reliable, regardless of the subject's gender, age at examination, disease duration, first symptom of disease, or years of education.

The results from this study are similar to those of a prospective study conducted by Richards and colleagues¹⁹ who reported high test-retest reliability ($ICC = 0.94$) among 45 patients living in New York City for age at onset of PD, as well as for tremor reported as the initial symptom ($ICC = 0.96$). They also concluded that these consistencies were not related to disease duration. The present study, which included a larger sample of individuals, ascertained from a broader geographic catchment area, i.e., North America, further demonstrate reliability in reporting age at onset of PD. Although these analyses do not confer validity, they do provide evidence that recall of such data is neither arbitrary nor appreciably influenced by confounding factors.

Previously, *parkin* gene screening was performed in families who either had at least one study participant whose age at onset of PD was reported on any of the three study instruments to be less than or equal to 45 or who had a positive lod score with a marker in the *parkin* gene.²⁰ Of interest, among the 42 subjects with the earliest age at onset, 13 of the subjects, from 8 different families, had a mutation(s) in the *parkin* gene. Hence, the lower reliability among the individuals with earlier age at onset of PD may be due to several sources. These sources include 1) the primary physician's limited familiarity with earlier onset PD and, therefore, the resulting lack of recorded documentation by that medical professional of disease onset; and 2) less typical clinical features of PD among the individuals with *parkin* mutations, resulting in a poorly documented age at disease onset. In either instance, it is important to note that the reliability for age

TABLE 3. Reliability estimates

Sample	Reliability
Overall (n = 149)	0.94
Gender	
Males (n = 89)	0.93
Females (n = 60)	0.94
Age at exam (yr)	
0–64 (n = 42)	0.84
65–74 (n = 70)	0.92
≥75 (n = 37)	0.93
Disease duration (yr)	
0–4 (n = 57)	0.98
5–9 (n = 38)	0.78
≥10 (n = 54)	0.92
First symptom of PD	
Tremor (n = 78)	0.91
Other (n = 70)	0.96
Education (yr)	
<12 (n = 31)	0.94
12 (high school graduate, n = 26)	0.91
13–15 (n = 36)	0.96
≥16 (college graduate, n = 56)	0.93

PD, Parkinson's disease.

at onset in the early onset group was not significantly different from that in the other two groups.

Data regarding age at onset was collected using different instruments and variable format. One fundamental methodological issue that was not addressed in our study was the source of the age at onset information. Only the SHQ captured specific data regarding the source of the information (i.e., subject, spouse, other). The FHQ did not specifically ask who provided the responses to the age at onset items. It is interesting to note that even the medical records did not typically include data regarding the source of information during the patient visit to a clinician. It certainly is possible that different sources have provided the age at onset information used in the analyses. A second methodological issue in this study design is the ascertainment bias introduced by including in the sample only subjects who have ages of onset and that these ages of onset must be less than the age at interview. This strategy may produce an upward bias in the estimate of reliability.

A potential limitation of this study is the use of data ascertained from individuals with familial PD. The recruitment criteria for this study were a sibling pair, both of whom were diagnosed with PD. Thus, it is possible that individuals having a previously diagnosed family member may seek medical care more rapidly than those without a positive family history of disease. Although this possibility may lead to a shorter duration between age at onset and age at diagnosis, this does not necessarily suggest that there should be greater reliability in the age at onset information between self-report and medical records. We do not anticipate that our use of sibling data has biased our results.

It is important both clinically and epidemiologically that the age at onset reported through the three instruments has very high reliability. This reliability suggests that age at onset information can be gathered through patient and family reports of age at onset rather than the sometimes tedious collection of all relevant medical records.

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APPENDIX

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