Parkinson Disease in Twins
An Etiologic Study

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THE IMPORTANCE OF INHERITANCE

In the origin of Parkinson disease (PD) has been debated for more than a century. In the early 1980s, interest in an environmental cause of PD was spurred by the identification of biological effects of the neurotoxicant 1-methyl-4-phenyl,1,2,3,6-tetrahydropyridine (MPTP). This relatively simple pyridine moiety induces most if not all of the signs and symptoms of PD in humans1 and experimental animals.2,3 Recently, the genetic hypothesis regained momentum with identification of mutations in the α-synuclein gene4,5 or linkage to a region on chromosome 2 in families with PD.6 Yet most cases of PD do not have affected family members’ and the α-synuclein mutation appears to be rare:8,9 Thus, whether genetic factors are important in typical PD remains in question.

To resolve this dilemma, we initiated the largest twin study of PD, to date, taking advantage of the National Academy of Sciences/National Research Council (NAS/NRC) World War II Veteran Twins Registry.10 This cohort is ideal for such a study, because these individuals have reached an age range of increasing risk for PD and were not selected for late-life diseases.

METHODS
Subjects and Evaluation

Ascertainment and Screening of the Cohort. When established, the NAS/NRC World War II Veteran Twins Registry consisted of 31,848 white male twins (15,924 pairs; 9,333 monozygotic [MZ], 7,554 dizygotic [DZ], and 2,437 with unknown zygosity).10 We attempted to contact all 19,842 individual twins (7,882 MZ, 9,699 DZ, and 2,261 unknown zygosity) believed to be alive in 1992 (FIGURE). The protocol was approved by the institutional review boards of all involved institutions. Twins not initially located were also identified by (1) querying the twin brother, (2) querying a previously provided contact, and (3) searching commercially available databases. Twins diagnosed as having parkinsonism were also sought by searching the medical databases of the Department of Veterans Affairs, the Health Care Financing Administration, and the National Death Index, and by referral from the study of dementia by Duke University, which is ongoing in a subgroup of the registry.11 Twins were asked by mail to volunteer for a telephone interview. A preaddressed refusal card was provided. When both twins were known to be dead, could not be located, or refused participation, the pair was excluded from further study. Participating

RESULTS

Of 268 twins with suspected parkinsonism and 250 presumed unaffected twin brothers, 193 twins with PD were identified (concordance-adjusted prevalence, 8.67/1000). In 71 MZ and 90 DZ pairs with complete diagnoses, pairwise concordance was similar (0.129 overall, 0.155 MZ, 0.111 DZ; relative risk, 1.39; 95% confidence interval, 0.63-3.1). In 16 pairs with diagnosis at or before age 50 years in at least one twin, MZ concordance was 1.0 (4 pairs), and DZ was 0.167 (relative risk, 6.0; 95% confidence interval, 1.69-21.26).

CONCLUSIONS

The similarity in concordance overall indicates that genetic factors do not play a major role in causing typical PD. No genetic component is evident when the disease begins after age 50 years. However, genetic factors appear to be important when disease begins at or before age 50 years.

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twins or proxy informants (for dead, refusing, or demented twins) received a brief interview screening for suspected parkinsonism, dementia, cerebrovascular disease, eye disease, cancer, and possible risk factors for these diseases.

**Suspected Parkinsonism.** Twins who reported a prior diagnosis of parkinsonism were classified as having suspected parkinsonism. Of the remaining twins, those with specific patterns of responses to screening questions received a second, semistructured interview with a nurse and were then classified by a neurologist (C.M.T.).

**Subjects Examined.** Subjects with suspected parkinsonism and their twin brothers were asked to volunteer for an in-person evaluation (Figure). Standardized evaluations, performed at home or in a medical center by 1 of 18 neurologists with expertise in PD, included a complete neurologic history taking and examination, the Unified Parkinson’s Disease Rating Scale, a standardized videotaped examination, and phlebotomy. When possible, each twin in a pair had a different examiner. Examiners were not informed of zygosity, although subjects could not be prevented from volunteering this information.

**Assigning a Final Diagnosis.** Core assessment program for intracerebral transplantations diagnostic criteria were used. Probable PD was defined as (1) the presence of at least 2 of the following signs: resting tremor, cogwheel rigidity, bradykinesia, or postural reflex impairment, at least 1 of which must be either resting tremor or bradykinesia, (2) no other cause of parkinsonism, (3) no signs of more extensive neurodegeneration indicating atypical parkinsonism, and (4) a clear-cut response to levodopa, if treated. Possible PD was defined in 1 of the following ways: (1) the presence of cogwheel rigidity and postural reflex impairment, no other cause of parkinsonism, and a clear-cut response to levodopa, but also with another clinical symptom or sign sometimes but not
always found in PD (eg, prominent dementia, severe dysautonomia).

**Final Diagnosis.** All in-person evaluations were reviewed independently by a second neurologist with expertise in PD, blinded to (1) zygosity, (2) disease status of the twin brother, and (3) the in-person examiner’s diagnosis. If the examining and reviewing neurologists agreed, this diagnosis was accepted. When there was disagreement, final diagnosis was established by consensus of 2 blinded neurologists with expertise in PD, who reviewed all available information. For dead or refusing twins, diagnostic criteria were applied using all available information (including medical records, death certificates, and proxy interviews). In our pilot work, twins serving as proxy informants correctly identified their twin brothers as having PD 86% of the time, with no false-positive identifications.

**Zygosity.** Whenever possible zygosity was determined by polymerase chain reactions using multiple markers of hypervariable single-locus short-tandem repeats.10 When DNA was not available for both twins, standard questions were used.20,21

**Analysis**
The primary concordance measure was pairwise concordance, the number of pairs in which both members had PD at final diagnosis, divided by the total number of pairs in which at least 1 twin had PD. Proband-wise concordance was calculated using the following formula: \[ \frac{2c_2 + c_1}{2c_2 + c_1 + d} \], where \( c_2 \) represents the number of discordant pairs in which both twins are probands, \( c_1 \) represents the number of pairs in which only 1 twin is a proband, and \( d \) represents the number of discordant pairs.32 Twins with suspected parkinsonism at screening who had final diagnoses of possible or probable PD were considered to be probands. Secondary analyses defined disease in the second member of a pair more broadly, when the first twin had PD. In these analyses, pairs were considered to be concordant if 1 twin had PD and the second had: (1) PD or any parkinsonian syndrome, (2) PD or essential tremor, (3) PD or dementia, or (4) PD or any of the preceding diagnoses. Concordance rates, risk ratios, cumulative incidence rates, and heritability22,23 were calculated for the entire sample, and in subgroups determined by zygosity, age at diagnosis (by decade), and younger age at diagnosis. Age at diagnosis was determined by the examining neurologist by interview, and corroborated by medical records when possible. Younger age at diagnosis was defined as diagnosis before age 51 years, reflecting the well-established near-exponential increase in incidence and prevalence of PD after age 50 years.24 Comparisons of subgroup characteristics used parametric or nonparametric analyses, as appropriate, using the commercial statistical software packages (SPSS, Version 6.1, SPSS Inc, Chicago, Ill, and Epi Info, Version 3.01b, Centers for Disease Control and Prevention, Atlanta, Ga).

**RESULTS**
Screening interviews were completed for 14 436 living twins (5994 MZ, 7071 DZ, and 1371 of unknown zygosity) (Figure). A total of 2689 proxy interviews were completed for those who were dead, were not located, or refused (960 MZ, 1517 DZ, and 212 unknown zygosity). Suspected parkinsonism was identified in 268 twins, 175 of whom had a final diagnosis of possible or probable PD. Of the 164 twin brothers of twins with suspected parkinsonism, 95 were examined and 18 were diagnosed as having PD. Medical records and/or in-depth interviews of family members were obtained for 122 of 149 subjects who were dead or refused examination.

In total, PD was diagnosed in 193 twins (158 probable, 35 possible), of whom 18 were newly diagnosed by study physicians. In the remaining 239 twins evaluated, diagnoses were: essential tremor (\( n = 49 \)), other neurologic disorders without extrapyramidal signs (\( n = 42 \)), progressive supranuclear palsy (\( n = 4 \)), drug-induced parkinsonism (\( n = 4 \)), Alzheimer-type dementia (\( n = 3 \)), vascular parkinsonism (\( n = 2 \)), diffuse Lewy body disease (\( n = 2 \)), Huntington disease (\( n = 1 \)), olivopontocerebellar atrophy (\( n = 1 \)), and striatoni- gral degeneration (at postmortem) (\( n = 1 \)). In 121, no neurologic disease was diagnosed. In 9 twin brothers of twins with PD, no diagnosis was possible because no medical records or proxy contact could be found. Thirteen twins with initial diagnoses of PD were assigned a different diagnosis at consensus review.

The overall prevalence of PD was 9.7/1000. Concordance-adjusted prevalence, in which only 1 member of a twin pair is counted to avoid overestimating prevalence, was 8.67/1000.

**Clinical Characteristics**
Mean age at PD diagnosis overall was 64.5 years (SD, 9.1 years; range, 25-79 years). No clinical characteristic showed statistically significant differences between groups defined by zygosity or both zygosity and age at diagnosis (\( P > .05 \), Table 1).

**Zygosity of Participants**
Zygosity was determined by polymerase chain reaction in 31 (44%) MZ and 43 (48%) DZ pairs. Zygosity determined by...
polymerase chain reaction differed from zyosity determined by questionnaire in 4 (5.4%) pairs; in each case presumed MZ pairs were found to be DZ.

Of 30 twins with suspected parkinsonism who refused to participate or were not located, 11 were presumed MZ, 14 DZ, and 5 unknown zyosity. For 28 screen-negative or control twins refusing or not located, 13 were presumed MZ, 14 DZ, and 1 of unknown zyosity.

Concordance and Heritability

Of the 172 twin pairs identified in which at least 1 twin had PD, 9 were excluded because no diagnostic information was available for 1 twin. In the 163 twin pairs for which diagnostic information was available for both brothers (71 MZ pairs, 90 DZ pairs, 2 of unknown zyosity), the overall pairwise concordance for PD was 0.129. In the 161 pairs with known zyosity, pairwise concordance was similar in MZ and DZ pairs overall (0.155 MZ vs 0.111 DZ) (Table 2). Pairwise concordance was virtually identical for MZ and DZ pairs with PD diagnosed after age 50 years (0.106 MZ vs 0.104 DZ). However, when PD began before age 51 years in at least 1 twin, MZ concordance was 1.00, and DZ concordance was 0.167. Although the numbers of concordant pairs increased overall when broader definitions of disease in the second twin were used, the risk ratios did not change substantially (Table 3).

Cumulative Incidence and Proportional Hazards Estimates in Concordant Pairs

Overall, the incidence of PD in the second member of a twin pair was 0.0019/person-year. Incidence rates of PD were not significantly different in MZ and DZ pairs. For pairs with diagnosis in the first twin after age 50 years, PD incidence was similar for the second twin in MZ and DZ pairs. In pairs with diagnosis before age 51 years in 1 brother, the second twin was 6 times more likely to develop PD in an MZ pair than in a DZ pair. Using a Coxl proportional hazards model, zyosity had no effect on the hazard of developing PD in the second twin overall, or for twins with diagnosis after age 50 years. For twins with diagnosis of PD in 1 twin before age 51 years, the hazard of PD in the second twin was greater in MZ than in DZ twins (hazard ratio, 9.5; 95% confidence interval, 1.7-52.4; P<.01).

Interval to Diagnosis in Second Twin

In both MZ and DZ concordant twin pairs, the interval between diagnosis of PD in the first and second brothers was similar (MZ: mean, 8.6 years and range, 2-28 years; DZ: mean, 9.7 years and range, 2-31 years). There was no statistically significant difference in mean interval to diagnosis of PD in the second twin when analyses were stratified by age at PD diagnosis.

Concordance for Previously Diagnosed Cases

Only 9 of 21 concordant pairs were identified as concordant before our examination. Using only these pairs, overall MZ concordance was 0.05 and DZ concordance 0.03 for pairs diagnosed after age 50 years. For pairs with at least 1 twin diagnosed before age 51 years, MZ concordance was 0.75 and DZ concordance 0.08.

**Table 2.** Concordance and Heritability for Parkinson Disease*  

<table>
<thead>
<tr>
<th>Concordant Pairs</th>
<th>Discordant Pairs</th>
<th>Pairwise Concordance</th>
<th>Probandwise Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZ</td>
<td>DZ</td>
<td>MZ</td>
</tr>
<tr>
<td>Overall</td>
<td>11</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>First twin diagnosed ≤50 y</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>First twin diagnosed &gt;50 y</td>
<td>7</td>
<td>2</td>
<td>58</td>
</tr>
</tbody>
</table>

*MZ indicates monozygotic; DZ, dizygotic; and CI, confidence interval. Superscript represents the number of pairs doubly ascertained.

**COMMENT**

Twin studies can be particularly useful in distinguishing the relative contributions of genetics and environment to the cause of a disease. If genetic factors are important, concordance in MZ twins, who are genetically identical, will be greater than in DZ twins, who share the same number of genes as other siblings (50% on average). If a disorder is exclusively genetic in origin, MZ concordance approaches 100%. At least 6 pairs of twins concordant for PD have been reported. These studies suggested that PD might be inherited, but the generalizability of these observations could not be determined without a population-based investigation.

In contrast to individual reports of concordant pairs, previous investigations of groups of twins failed to find evidence of a genetic component for PD. However, each of these studies had methodological limitations, including Johnson et al., in a critical review of the literature, to conclude that no study was definitive. The current study was designed to overcome these limitations. First, all of the published studies had relatively few affected pairs. The current study represents more twin pairs with PD than in all previous publications combined. Second, twins included in prior reports were relatively young, so that actual cases of PD may have been missed. In contrast, all subjects in the current study were 65 years or older when screened, an age at high risk of PD. Third, prior studies had potentially biased ascertainment. In contrast, the population we studied was relatively unselected, having been assembled decades ago based only on twin and vet...
geran status. Participation rates at all stages of the ascertainment process were high, further minimizing the chance of ascertainment bias. In fact, the prevalence of PD in this cohort overall is similar to that seen in other community-based studies. 36-41 Fourth, in several prior studies, twins were not examined, so diagnostic accuracy was uncertain. All cases in this study were diagnosed using established diagnostic criteria, by neurologists with special expertise in PD. Importantly, twins were diagnosed independently without knowledge of zygosity or of the presence of disease in any family member, a refinement not used in any of the previously published studies.

Having addressed these methodological issues, we observed no overall difference in concordance for PD between MZ and DZ pairs. This finding is inconsistent with a genetic cause for typical PD, particularly when the disease begins after age 50 years. This study also addressed a previously voiced concern that genetic patterns might be obscured by the application of overly stringent diagnostic criteria. 42-43 We performed additional analyses using progressively broader definitions of disease in the second member of a twin pair. Using this approach, we still failed to observe an increased concordance in MZ pairs.

Despite our attention to methodological issues and straightforward results, this study did have potential limitations. First, it was cross-sectional. Without follow-up observation, potential biases inherent in observations made at a single time point cannot be fully addressed. For example, an underestimation of MZ concordance for PD might result if the interval to diagnosis in the second member of an MZ pair were longer than the interval in a DZ twin. However, our current results provide no support for this possibility, since we found the average interval to diagnosis of disease in the second brother to be similar for MZ and DZ twins, even when results were stratified by the diagnosis age of the twin first affected. Similarly, using Cox regression modeling to control for differential follow-up, we did not find the risk of concordance to be greater in MZ twins overall, or in those with diagnosis after age 50 years. Nonetheless, the mean age at diagnosis in our twins was about 65 years, and the median, 67 years. More than 25% were diagnosed after age 70 years. Since an average of nearly 10 years elapsed before the second twin was diagnosed in concordant pairs, additional concordant pairs are likely to be identified with continued follow-up. Whether the distribution of disease will differ by zygosity in cases diagnosed at an older age remains unknown.

A second potential limitation of the study is the possibility of diagnostic misclassification, especially of newly diagnosed PD, since atypical parkinsonism may not be apparent early in the clinical course. Parkinson disease was newly diagnosed in 18 cases, but excluding these did not alter our results (data not shown). In addition, study neurologists knew they were evaluating twins with possible PD and could have been predisposed to diagnose the disease in the face of mild clinical signs more often than they would outside of such a study. We therefore used a standardized consensus method to assign diagnoses to minimize this potential bias. However, greater diagnostic precision can only be achieved after extended clinical follow-up, and, ultimately, postmortem examination.

A final limitation of this study is the fact that the cohort was exclusively white men living in the United States. The applicability of these findings to women and members of other racial or national groups remains uncertain.

While the current study suggests that typical PD diagnosed after age 50 years has no genetic component, quite the opposite was observed in the 16 pairs in which PD was diagnosed before age 51 years in at least 1 twin. In these, all 4 of the MZ pairs were concordant, but only 2 of 12 DZ pairs. This pattern strongly supports a primarily inherited cause of early-onset PD. This observation is consistent with observations in many families with parkinsonism, in which younger age at disease onset is often observed. 44 Therefore it seems reasonable to conclude that searches for a genetic component or form of parkinsonism might be best directed toward subjects with younger-onset disease.

While the observation of 100% concordance in the younger-onset MZ pairs is compelling, only 4 such pairs were identified, and precision is low. Conceivably, an investigation including more twins with young-onset disease could yield a different result.

Although 12,006 twins in the original cohort died before 1992, because PD is rare before age 50 years, a maximum of 6 young-onset cases would have been missed by not including these twins. Even if 6 young-onset cases were added to our sample, our current conclusions would be supported.

Finally, it is important to note that while increased concordance for PD in the younger-onset MZ twins is consistent with a genetic origin of disease, shared environment in these twins could produce the same pattern. Until specific genetic or environmental factors are identified, the underlying cause of this pattern cannot be tested.

**Table 3. Effect of Broader Definition of Disease in Second Member of a Twin Pair on Pairwise Concordance**

<table>
<thead>
<tr>
<th>Definition of Concordance</th>
<th>Pairwise Concordance</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson disease in twin 1 and Parkinson disease in twin 2</td>
<td>0.129 0.156 0.111</td>
<td>1.39 (0.63-3.10)</td>
</tr>
<tr>
<td>Parkinson disease in twin 1 and Parkinson disease or other parkinsonism in twin 2</td>
<td>0.276 0.338 0.233</td>
<td>1.45 (0.88-2.38)</td>
</tr>
<tr>
<td>Parkinson disease in twin 1 and Parkinson disease or other parkinsonism in twin 2</td>
<td>0.135 0.169 0.111</td>
<td>1.52 (0.7-3.32)</td>
</tr>
<tr>
<td>Parkinson disease in twin 1 and Parkinson disease, essential tremor, other parkinsonism, or dementia in twin 2</td>
<td>0.294 0.366 0.244</td>
<td>1.50 (0.93-2.41)</td>
</tr>
</tbody>
</table>
In summary, our findings suggest that heredity is not a major etiologic component in most cases of PD, particularly in typical cases beginning after age 50 years. This observation is of obvious significance to the families of persons with PD, most of whom need not assume that they have inherited the gene for PD. Our findings are also of potential use in developing research priorities. Since purely genetic PD appears to be rare, investigations of genetic forms of parkinsonism, such as families with multiple affected generations, will be important primarily as a means of identifying the underlying disease mechanisms that may provide clues to the cause of the more common nongenetic PD. The identification of the nongenetic risk factors for PD represents the next challenge. Hopefully, such studies will take us a step closer to finding the cause of PD.

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REFERENCES


