Phenotypic Commonalities in Familial and Sporadic Parkinson Disease

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Background: Parkinson disease (PD) is a clinically well-documented neurodegenerative disorder. However, the mechanism or mechanisms of its phenotypic expressions are still unknown.

Objective: To compare phenotypes by examining demographic and clinical features of patients with familial PD and sporadic PD and with or without a family history of PD.

Design: Historical review of patients with sporadic PD in clinic-based samples and individual patients diagnosed with PD from families whose linkage to mutations or loci has been identified.

Setting: Movement disorder clinic in a referral center.

Patients: A total of 1277 patients with sporadic PD and 40 patients with familial PD.

Main Outcome Measures: Clinical features, including distribution by sex, initial motor symptom, location of initial motor symptom, and frequency of asymmetric motor symptoms.

Results: Despite different etiologic backgrounds, both familial and sporadic PD exhibited several interesting commonalities, including a higher incidence in men, tremor as the initial motor symptom (predominantly involving the upper extremities), and asymmetric parkinsonism during disease course.

Conclusions: The increased incidence of parkinsonism in men with familial PD suggests that the sex disparity is more likely the result of a protective effect against development of PD in women than of an increased risk in men that is associated with environmental factors. Phenotypic similarity among familial and sporadic PD indicates that a similar topographic distribution of the nigrostriatal lesion exists in patients with either form of PD regardless of apparent genetic influence.

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Genetic studies have provided new insights into the etiopathogenic mechanisms of Parkinson disease (PD). In particular, the discovery of 6 genes (SNCA, parkin, UCHL1, PINK1, DJ1, and LRRK2) in familial parkinsonian kindreds has enhanced interest in the genetic contribution to this disorder. Interactions among genetic and environmental factors may play an important role in the development of sporadic PD. However, the exact causes of degeneration in the nigrostriatal dopaminergic system are unknown, as are the causes of the occurrence of α-synuclein-positive Lewy bodies, which are the pathologic hallmark of PD, and their relationship to the clinical phenotype of PD. Moreover, patients with PD have some puzzling demographic and clinical characteristics, including increased risk for development of the disease in men and asymmetric onset and presentation of motor symptoms. These 2 characteristics are acknowledged in sporadic PD, but their presence in familial kindreds has not been studied formally.

Among familial parkinsonian kindreds where linkage to mutations or loci has been identified, the clinical and pathologic features of patients from a German-American kindred (family C) linked to chromosome 2p13 (PARK3) and a Greek-American kindred (family H) associated with a missense SNCA mutation on chromosome 4q21 (PARK1) are inseparable from those in patients with PD. Therefore, to evaluate phenotypes among patients with familial or sporadic PD, specifically in regard to sex distribution and motor symptoms, we compared demographic and clinical characteristics among patients diagnosed with PD from families C and H with those among patients with sporadic PD.
The pedigrees have been published previously.7,8 Genealogical studies included evaluation of historical material, family records, and interviews with family members. After approval of the study by the Mayo Foundation Institutional Review Board, medical and historical records were collected and reviewed.

The examination instruments for available patients included a standardized medical history, neurologic examination, the Unified Parkinson Disease Rating Scale, and the Mini-Mental State Examination. Laterality of parkinsonism was assessed on the basis of available clinical records. Clinical data of deceased patients were obtained from available medical records.

**FAMILIAL PD**

Three hundred seven patients from 16 large kindreds with familial parkinsonism (with 10 or more affected members) have been followed up longitudinally at Mayo Clinic, Jacksonville, Fla (Z.K.W.). Genetic studies of these kindreds demonstrated linkage for PARK1 in family H (A53T mutation),9 for PARK8 in families A and D (Y1699C and R1441C mutations, respectively),10 and for PARK3 in family C (mutation unknown).7 Linkage or mutations have not yet been found for the other 12 kindreds. Consequently, we selected families C and H, which had sufficient information available for the assessment, as the representatives of familial parkinsonism because the pathologic findings in affected members from these 2 families were indistinguishable from those observed in patients with sporadic PD. Families A and D were excluded from analysis owing to pleomorphic pathologic features.9 The pedigrees have been published previously.7,8 Genealogical studies included evaluation of historical material, family records, and interviews with family members. After approval of the study by the Mayo Foundation Institutional Review Board, medical and historical records were collected and reviewed.

The genealogical study of family C identified 355 persons who were at risk for familial PD. The male-female ratio of those at risk was 1.1:1.0, respectively (170 men and 185 women). The penetrance of the mutation appears to be low, estimated at less than 40%.6 Similarly, in family H, we identified 119 persons at risk for familial PD, with a male-female ratio of 1.1:1.0, respectively (63 men and 56 women). The penetrance of the mutation in family H was estimated at 85%. However, owing to geographic and personal factors, only 60 (17%) and 18 (15%) of the individuals from families C and H, respectively, who were genealogically at risk for familial PD participated in the genetic study by donating a blood sample.

The mean age at symptom onset was 56.8 years (range, 25-73 years) in family C and 52.9 years (range, 31-71 years) in family H. The mean disease duration was 20.6 years (range, 2-53 years) in family C and 52.9 years (range, 31-71 years) in family H.

The distribution of familial PD is shown in Table 1. With a difference score of 1 or more determined to be those with asymmetric parkinsonism. On the basis of the collected data, we classified patients as either having or not having a family history of PD.

To compare the phenotypes of patients with familial and sporadic PD, we tabulated all of the available information, including distribution by sex, initial motor symptom, location of initial motor symptom, and frequency of patients with asymmetric motor symptoms. Moreover, we performed the same comparison among patients with familial PD and patients with sporadic PD either with or without a family history of PD. The Fisher exact test was used to compare the distribution frequency of each category. The level of significance was set at P<.05.

**RESULTS**

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The ratio of affected men to affected women was similar between family C and sporadic PD, for about a 2.0-fold higher prevalence in men (Table 1). Family H also had a higher prevalence of PD (1.6-fold) in men. The distribution of sporadic PD predominantly in men was found regardless of a family history of PD. There was no significant difference in sex distribution among groups.

Most individuals with either familial or sporadic PD had tremor as the initial motor symptom (54% of the patients with familial PD and 48% of those with sporadic PD), which initially appeared in the upper extremities (47% of the patients with familial PD and 37% of those

| Table 1. Distribution by Sex of Patients With Familial Parkinson Disease From Families C and H Compared With Patients With Sporadic Parkinson Disease |
|-----------------|-----------------|-----------------|
|                  | Familial PD     | Sporadic PD     |
|                  | Family C        | Family H        | (n = 1277) | With Family History of PD (n = 190) | Without Family History of PD (n = 1087) |
| Men, No.         | 15              | 11              | 847       | 127                          | 720                           |
| Women, No.       | 7               | 7               | 430       | 63                           | 367                           |
| Male-female ratio| 2.1             | 1.6             | 2.0       | 2.0                          | 2.0                           |

Abbreviation: PD, Parkinson disease.
with sporadic PD) (Table 2). Most patients (95% of the patients with familial PD and 87% of those with sporadic PD) reported asymmetric motor symptoms. We found no statistically significant differences in the distribution by sex or initial motor symptom and location between familial and sporadic PD (either with or without a family history of PD).

Table 2. Clinical Characteristics of Patients With Familial or Sporadic Parkinson Disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With Familial PD, No. (%)</th>
<th>Patients With Sporadic PD, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 40)</td>
<td>With and Without Family History of PD (n = 1277)</td>
</tr>
<tr>
<td>Initial motor symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>15 (54)*</td>
<td>613 (48)</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>7 (25)*</td>
<td>364 (28)</td>
</tr>
<tr>
<td>Rigidity</td>
<td>6 (21)*</td>
<td>67 (5)</td>
</tr>
<tr>
<td>Postural instability or gait disturbance</td>
<td>0</td>
<td>138 (11)</td>
</tr>
<tr>
<td>Other†</td>
<td>0</td>
<td>95 (8)</td>
</tr>
<tr>
<td>Missing</td>
<td>12 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Location of initial motor symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right upper extremity</td>
<td>9 (47)‡</td>
<td>473 (37)</td>
</tr>
<tr>
<td>Left upper extremity</td>
<td>7 (37)‡</td>
<td>278 (22)</td>
</tr>
<tr>
<td>Bilateral upper extremities</td>
<td>1 (5)‡</td>
<td>116 (9)</td>
</tr>
<tr>
<td>Right lower extremity</td>
<td>1 (5)‡</td>
<td>53 (4)</td>
</tr>
<tr>
<td>Left lower extremity</td>
<td>1 (5)‡</td>
<td>44 (3)</td>
</tr>
<tr>
<td>Bilateral lower extremities</td>
<td>0‡</td>
<td>177 (14)</td>
</tr>
<tr>
<td>Other§</td>
<td>0‡</td>
<td>136 (11)</td>
</tr>
<tr>
<td>Missing</td>
<td>21 (52)</td>
<td>0</td>
</tr>
<tr>
<td>Asymmetric motor symptoms</td>
<td></td>
<td>18 (95)</td>
</tr>
<tr>
<td>Missing</td>
<td>21 (52)</td>
<td>61 (5)</td>
</tr>
</tbody>
</table>

Abbreviation: PD, Parkinson disease.
*Percentages reflect a population size of 28 because data were not available for 12 patients.
†Other initial symptoms included pain, speech disturbance, and involuntary movements (eg, dystonia or action tremor).
‡Percentages reflect a population size of 21 because data were not available for 21 patients.
§Other locations of initial symptom included right side, left side, face, head, and neck.
||The total numbers of patients available for tabulation were 19 patients with familial PD, 1216 patients with sporadic PD, 184 patients with sporadic PD and a family history of PD, and 1032 patients with sporadic PD but no family history of PD.

Patients with PD from both family C and family H and all of the patients with sporadic PD showed a similar sex distribution. The 1.6- to 2.0-fold higher distribution in men is consistent with previously described large-scale epidemiologic studies. A similar increased incidence of PD in men was also present in the Contursi kindred (with a missense A53T gene mutation [PARK1]) and the Iowan kindred (with an SNCA gene triplication [PARK4]), both of which had familial parkinsonism and Lewy body pathology (Table 3).

Regarding the sex incidence, environmental factors (eg, toxic exposures associated with farmwork) or head injury, which could reflect a male lifestyle, are likely to create an increased risk for PD in men. However, these associations are controversial. Alternatively, the neuroprotective effects of estrogen or other hormonal influences in women that potentially help guard against development of PD may contribute to the sex disequilibrium. The increased incidence of parkinsonism in men in families C and H under circumstances of equivalent genetic risk, and probably in environmental exposures similar to those of women, provides some evidence for a hypothesis to explain the disproportionate sex incidence in PD. This scenario suggests that the sex disparity is more likely to result from a relative protective effect against development of PD in women than from an increased risk in men that is associated with environmental factors.

To our knowledge, the similar distributions of the initial motor symptom and its location among familial and sporadic PD are also newly discovered results. These findings indicate a similar topographic distribution of the nigrostriatal lesion leading to symptomatic disease occurrence in patients with either form of PD regardless of apparent genetic influence. There were no patients with familial PD who initially had postural instability or gait disturbance. In patients who initially had rigidity, the frequency of familial PD was 4 times higher than that of sporadic PD, but no statistically significant difference was found (the small sample size may have limited power in these comparisons). Therefore, the results described here regarding initial motor symptoms and their location between familial and sporadic PD may require confirmation in further large-scale studies.

More than 90% of patients with parkinsonism in both family C and family H exhibited asymmetric parkinsonism during the course of the disease, which is identical to the distribution of the incidence in the sporadic PD cohort. It should be noted, however, that a gold-standard definition of asymmetry has not been estab-
lished. Not surprisingly, estimates of asymmetry vary considerably from one study to the next, typically ranging from 40% to 60%. In the current study, asymmetry was determined qualitatively for the patients with familial PD and quantitatively for the patients with sporadic PD. Nonetheless, there is no dispute that asymmetric motor symptom presentation is a common feature not only in sporadic PD but also in familial PD. Given the seemingly homogeneous presence of genetically driven mechanisms throughout the entire brain, the similarity is curious if one assumes that these should symmetrically affect neural tissue and lead to disease. However, just as we have suggested that asymmetric features in sporadic PD may be determined by intrinsic factors that establish laterality in humans (eg, handedness), the same type of mechanisms may be operative in familial disease.

In addition to patients with PARK1, PARK3, and PARK4, patients from kindreds linked to PARK5 (UCH1 gene), PARK8 (LRRK2 gene), and PARK11 may also show late-onset and levodopa-responsive parkinsonism similar to sporadic PD. Since kindreds linked to PARK5 and PARK11 were not followed up in our clinic, we were unable to evaluate the demographic and clinical characteristics in this study. However, the existence of histopathologic abnormalities related to sporadic PD is still uncertain in PARK5 and PARK11. The histopathologic abnormalities associated with PARK8 or LRRK2 vary considerably; not only are Lewy bodies present in the brain, but tau accumulation and nigral degeneration without any specific features are also present there. Therefore, we did not enroll families A and D linked to PARK8 in the present demographic and clinical comparisons. A recent study found that LRRK2 mutations can be detected in individuals with PD with no family history of parkinsonism whereas PARK5 and PARK11 are found in PD when there is a clinically significant family history. We did not perform a mutation search for PARK8 in our sporadic PD samples. However, patients with an LRRK2 mutation may exist in a small proportion of the sporadic PD population. At the present time, clinical genetic testing is commercially available for only 2 of 6 known PD genes, PARK2 and PARK7. These genetic studies are not routinely performed, but they can be done in select cases by patient request and after appropriate counseling.

Several important commonalities in the demographic and clinical features of familial and sporadic PD in this preliminary study may provide insights into the mechanisms of phenotypic expression of PD. Because patients with parkinsonism resembling idiopathic PD from kindreds with identified linkage to mutations or loci are extremely rare, the number of subjects with familial PD in our study was small. Therefore, further large-scale comparative studies involving more kindreds with familial parkinsonism that closely resembles idiopathic PD both clinically and pathologically are required to assess our observations and further delineate the mechanisms that are central to the development of the PD phenotype.

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