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Clinical Characteristics in Early Parkinson's Disease in a Central California Population-Based Study

Gail A. Kang, MD[1,2], **Jeff M. Bronstein, MD, PhD**[1,2], **Donna L. Masterman, MD**[1,2], **Matthew Redelings, MPH**[3], **Jarrod A. Crum, MPH**[3], and **Beate Ritz, MD, PhD**[3,*]

[1]Department of Neurology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA

[2]Greater Los Angeles Veterans Administration Medical Center, Los Angeles, California, USA

[3]Department of Epidemiology and Environmental Health Sciences, UCLA School of Public Health, Los Angeles, California, USA

Abstract

There is considerable variation in the phenotypic appearance of individuals with idiopathic Parkinson's disease (PD), which may translate into differences in disease progression in addition to underlying disease etiology. In this publication, we report on the demographic and clinical characteristics of 162 individuals diagnosed with clinically probable PD from January 1998 to June 2003 who resided in predominantly rural communities in central California. The majority of the subjects were Caucasian, male, and between 60 and 79 years of age. The akinetic–rigid and tremor-dominant subtypes were more common than the mixed subtype. The majority of subjects displayed motor signs of rigidity (92.0%), bradykinesia (95.7%), and gait problems (87.0%), whereas less than half (43.3%) of the subjects displayed a tremor. Three fourths of patients received a Hoehn and Yahr Scale score of Stage 2 or higher. One third of the patients were treated with levodopa, and patients under 60 years of age were more likely to be treated with dopamine agonists. Within 3 years after first diagnosis, 13% of subjects showed some signs of depression and 17% of subjects met criteria for mild dementia. Among our subjects, 17.3% reported a family history of PD in first- or second-degree relatives,15.4% a family history of essential tremor, and 14.2% of Alzheimer's disease. This study represents the most extensive phenotypic description of rural U.S. residents in the initial stages of PD who were recruited in a population-based manner; future follow-up may provide valuable information regarding the prognostic indication of these symptoms/signs and improve our understanding of the underlying etiology of PD.

Keywords

idiopathic Parkinson's disease (PD); phenotypic description; disease progression; etiology; population-based study

The neurologic community agrees that the core features for diagnosing idiopathic Parkinson's disease (PD) clinically are resting tremor, bradykinesia, rigidity, and postural instability. However, in individual patients there is considerable variation in the expression and predominance of each classic clinical sign and also in accompanying symptoms and disease course. Furthermore, there are many aspects of motor and nonmotor function in PD

*Correspondence to: Dr. Beate Ritz, UCLA School of Public Health, Box 951772, 650 Charles E. Young Drive, Los Angeles, CA 90095-1772. britz@ucla.edu.

that contribute to quite heterogeneous disease phenotypes. Some variations in presentation and course of disease may not only help to distinguish phenotypical subtypes that require treatment modifications and have different prognoses but, in addition, may reflect differences in underlying disease etiology, including varying responses to environmental and genetic susceptibility factors. Geneticists recently pointed out the importance of thoroughly documenting phenotype for the study of genetic contributions to many complex diseases such as asthma and adult-onset diabetes when studying gene to environment and gene to gene interactions.[1] Thus, with genetic studies of PD accumulating over the past 5 years, it may be more and more important to document and follow PD phenotypes at different stages of disease carefully to evaluate whether they may be linked to neuroanatomical, genetic, environmental, and treatment differences.

To date, only six studies conducted in the United States—Rochester NY,[2] Hawaii,[3] Olmsted County MN,[4] Manhattan NY,[5] Northern California Kaiser Permanente,[6] and the Harvard Nurses Health and Health Professionals Cohorts[7]— have enrolled more than 50 new-onset PD patients in a population-based and unselected manner such that they represented all newly diagnosed PD patients in a community or otherwise well defined population. However, these studies have usually not been able to provide a detailed description of the clinical characteristics of its population, because this requires movement disorder specialists to examine all patients identified in a large population or large geographic area in a standardized manner.[5,7–9] A few epidemiological studies that enrolled prevalent cases with variable disease duration have described patients' clinical features in more detail,[10,11] but most extensive phenotypical characterizations to date have only been documented for clinical samples from highly selected referral centers and tertiary care facilities specialized in movement disorders or in clinical trials in which patient volunteers were required to meet specific case screening protocols.[12–14] Most patients had suffered from the disease for variable durations at the time of examination. Due to the selectiveness of clinical samples, the patients in these studies are not representative of all PD patients in a community and do not allow for accurate description of clinical phenotypes seen relatively early in the course of disease in a random sample from all PD patients in a community. Here, we have the unique opportunity to present a description of the clinical phenotypes for a sample of rural patients soon after the first diagnosis of PD in a community setting.

These patients were identified for a population-based study of newly diagnosed (here defined as within 3 years of first diagnosis) cases of PD in three mostly rural Californian counties to investigate the interaction between genetics and environmental susceptibility. To date, we have enrolled and characterized 193 cases (162 probable PD, 31 possible PD) representative of mostly noninstitutionalized newly diagnosed patients in these counties who received a PD diagnosis between January 1998 to June 2003 that was confirmed by clinical examination performed by one of our movement disorder specialists (J.B. and D.M.). Clinical characteristics evaluated included motor and cognitive function, degree of disability, presence of depression, family history of PD, essential tremor (ET), Alzheimer's disease (AD), medication usage, and other chronic illnesses preceding or concurrent with PD diagnosis.

SUBJECTS AND METHODS

Subject Recruitment

We used a population-based approach, drawing from the populations of Fresno, Tulare, and Kern Counties, California. With the help of neurologists practicing in or nearby this region, we recruited PD cases among current residents. Altogether, 28 (90%) of the 31 practicing neurologists in these counties who provide care for PD patients participated in this study. Furthermore, we solicited collaboration from large medical groups (such as Kaiser

Permanente, Kern and Visalia Medical Center, and the Veteran's Administration), PD support groups, local newspapers, and local radio stations that broadcast public service announcements. Participating neurologists notified their patients about the study through mailings to all PD patients (for example, identified by their support staff as having a PD ICD-9 code of 332.0 on their billing information) and/or passing out study brochures to patients at office visits. PD support groups in Bakersfield, Visalia, and Fresno distributed information about our study to their members, and our study's neurologists and personnel attended local support group meetings to recruit new-onset patients. Based on the age–gender distribution for the three counties reported in the 2000 U.S. census and age-gender–specific PD incidence rates reported by Van Den Eeden and colleagues (2003) for Northern California Kaiser enrollees,[6] we estimated that we were contacted by approximately 60% of all potential new-onset PD cases that resided in these counties from January 1998 to June 2003. Of 766 patients who contacted us initially, 55% were ineligible because of their first PD diagnosis date falling outside of this time frame. Moreover, 10% died or were too ill to be examined and another 13% withdrew before seeing our study movement disorder specialist. The percentage of those who died or were too ill to participate increased from 2% in those under 60 years of age to 14% in those 80 years old and older. Finally, among those screened and/or examined by our movement disorder specialists, 20% did not have PD according to our diagnostic criteria. After excluding patients found to be misdiagnosed as PD from the denominator of all eligible PD patients and assuming that 80% of those who died and withdrew truly had PD and thus would have been eligible, we examined and interviewed 76% of PD patients who contacted us and were eligible. All procedures were approved by the UCLA Ethics Committee for Research of Human Subjects.

Case Definition

Cases were all individuals who (1) had been diagnosed with PD for the first time by a physician within the past 3 years; (2) were residents of Fresno, Kern, or Tulare Counties and had lived in California for at least 5 years; (3) had been seen by UCLA movement disorder specialists and had been confirmed as having clinically "probable" or "possible" PD; (4) did not have any other diagnosed neurological condition or serious psychiatric condition (including bipolar disorder, schizophrenia, or dementia before motor symptom onset); (5) were not in the last stages of a terminal illness; (6) were willing to participate. The criteria for a diagnosis of either clinically probable or possible PD were (I) presence of at least two of the following signs: bradykinesia, cogwheel rigidity resting tremor, at least one of which must have been resting tremor or bradykinesia; (II) no suggestion of a cause for another parkinsonian syndrome, such as trauma, brain tumor, infection, cerebrovascular disease, or other known neurological disease or treatment in the past with dopamine-blocking or dopamine-depleting agents; (III) No atypical features such as prominent oculomotor palsy, cerebellar signs, vocal cord paresis, severe orthostatic hypotension, pyramidal signs, amyotrophy, or limb apraxia; (IV) asymmetric onset; (V) if treatment with levodopa had been initiated, symptomatic improvement after treatment.

Probable cases met Criteria I to IV plus/minus V. Possible cases had at least one sign from Category I and fulfilled criteria described in II and III. The criteria of Hughes and associates[15] previously used[6] includes postural reflex impairment under Category I. However, we excluded this sign as a criterion because it usually occurs late in PD but may typically occur early in other parkinsonian disorders (i.e., multiple system atrophy, vascular parkinsonism).

Data Collection

Eligibility was assessed and basic demographic data were collected during telephone screening interviews or by mail for those patients without telephone service. UCLA

movement disorder specialists examined all eligible patients willing to participate and administered the Motor portion of the United Parkinson's Disease Rating Scale (UPDRS)[16] and assigned patients a score on the Modified Hoehn and Yahr Scale. Our movement disorder specialists examined patients 1 to 3 years from the initial time of PD diagnosis by a physician. Whenever possible, examinations were performed when patients were in the *off* state (n = 117; 72.2%) and had not taken L-dopa or other PD medications for at least 12 hours. Participants provided blood samples (results not reported here), completed medical history forms, and responded to the 15-Question Yesavage Geriatric Depression Scale (GDS)[17] and the Mini-Mental State Exam (MMSE).[18] After completing this evaluation, demographic and risk factor data were collected during telephone interviews by interviewers blinded to the case/control status of interviewees.

Standardized Instruments

We used items from the motor portion of the UPDRS to define presence of speech deficits, abnormal facial expression, resting tremor, action tremor, rigidity, bradykinesia, gait, and posture[16] and used the modified Hoehn and Yahr Scale (five-point scale) to assess PD-related disabilities. For mental function, we relied on the Mini-Mental State Examination,[18] and for the evaluation of depression, we used the short 15-item GDS.[17] Patients were subtyped into one of three clinical groups following the method proposed by Schiess and coworkers,[12] a modification of Jankovic's classification system.[13] Our method varied from that of Schiess and colleagues in that we did not include postural instability and gait difficulty in our calculation as we believed these conditions were more applicable to patients with advanced PD and we relied only on UPDRS III items, similar to Korchounov and associates 2004. The three subtypes were (1) akinetic–rigid; (2) tremor-dominant; and (3) mixed (features of akinetic –rigid and tremor). These classifications were derived from the UPDRS-motor score data collected by UCLA movement disorders specialists. Subtypes were defined according to the ratio of each patient's UPDRS III Tremor score (sum of Items 20 and 21 divided by 4) to his/her mean UPDRS akinetic/rigid score (sum of items 22–27 and 31 divided by 15) chosen in this manner to make our classification most comparable to the method of Schiess and coworkers such that (1) a ratio = 1.0 equals tremor-dominant, (2) a ratio = 0.80 equals akinetic–rigid, and (3) a ratio between 0.80 and 1.0 equals mixed.

Statistical Analyses

We are presenting our data mostly in a descriptive manner, but we used logistic regression models and calculated odds ratios (ORs) and 95% confidence intervals (CIs) to adjust for age, gender, and MMSE score when examining whether the odds of having a family history of PD, ET, or AD, several comorbid diseases, a low score on the GDS or MMSE, or a high score on the Hoehn and Yahr Scale differed according to PD subtype. All dependent (response) variables were treated as dichotomous (yes/no: family history, comorbid condition, being above or below a certain score for the GDS, MMSE, and Hoehn and Yahr Scale).

RESULTS

Demographic information for the 162 patients with probable PD and 31 patients with possible PD we identified and enrolled, and data collected are presented in Table 1 (note: all results presented in the remaining tables and text pertain to patients with probable clinical PD only). A small male predominance was observed in patients diagnosed before 80 years of age with a somewhat stronger one in the oldest age group (male/female rate ratios based on the population age distribution reported in the 2000 census: < 60 years, 1.39; 60 –79 years, 1.43; 80+: 3.21).

Most screened patients who were ineligible reported that their PD diagnosis preceded our inclusion date of 1998. However, 35 patients, who initially in our telephone screening qualified as eligible for enrollment in our study, were determined not to have PD when examined by the UCLA Movement Disorders specialist. The most frequent neurological diagnoses of these patients were ET (n = 5), vascular parkinsonism (n = 5), parkinsonism secondary to medication use (n = 4), progressive supranuclear palsy (n = 3), and diffuse Lewy Body disease (n = 3). Other diagnoses included multiple system atrophy, restless legs syndrome, dementia, and anxiety disorder. In 5 patients, the underlying neurological condition could not be determined.

The majority of male and female patients were assigned to the akinetic–rigid or tremor-dominant subtypes, whereas relatively few patients qualified for the mixed subtype (Table 2). Patients in the akinetic–rigid subtype were somewhat older. The majority of patients displayed motor signs of rigidity, bradykinesia, and gait problems (Table 3). Less than half displayed tremor and more than half presented with speech abnormalities. Postural instability was most common in the oldest patients. Three quarters of our patient population received a modified Hoehn and Yahr Scale score of Stage 2 or higher at the initial examination (i.e., on average 1.5 years after first diagnosis by a physician), indicating that parkinsonian signs were present bilaterally (Table 4). A slightly higher percentage of akinetic–rigid and mixed patients received Modified Hoehn and Yahr scores of Stage 2 or higher (akinetic–rigid, 78%; mixed, 74%; tremor-dominant, 66%). Patients in the oldest age group (>80 years) had a threefold higher odds of having a score of Stage 2 or higher; however, the 95% confidence intervals for the odds of scoring 2 or higher on this scale by PD subtypes and by age were wide and included the null value, thus precluding conclusions concerning the influence of age and subtype on Hoehn and Yahr staging.

Approximately one third of all patients were treated with L-dopa (Table 5), and approximately one third were on dopamine agonist monotherapy. Very few patients received treatment with a catechol-*O*-methyltransferase inhibitor. There were 19 patients taking Eldepryl, and 6 patients were receiving trihexyphenidyl. A total of 30 (19%) did not take any PD medications. Of these 30 patients not taking PD medications, 11 had a Hoehn and Yahr score of ≥2.5; 5 of these patients did not a neurologist and 1 patient did not take prescribed medications because of inability to pay for them. The distribution of PD subtypes was similar for the patients who took PD medications (akinetic–rigid, 50% [66 of 132]; mixed, 11% [14 of 132]; tremor-dominant, 39% [52 of 132]); and for those patients who did not take PD medications (akinetic–rigid, 43% [13 of 30]; mixed, 17% [5 of 30]; tremor-dominant, 40% [12 of 30]).

Mean GDS scores ranged from 1.5 to 3 and were fairly similar for PD subtype, gender, and age. In our study sample, 37 (23%) probable PD patients reported having taken antidepressant medication. Most of these patients reported initiation of these medications within the past few years before the time of our examination, and 21 (13%) scored ≥7 points on the GDS, indicating that they may suffer from depression; statistical analysis by logistic regression did not show any increased odds by age, gender, or PD subtype comparing patients above and below the cutoff of 7. On the MMSE, 28 (17%) patients received a score of 23 or less, suggesting the presence of dementia. MMSE scores were fairly similar across various PD subtypes, although men with the tremor-dominant subtype received a slightly lower mean score. Men who were over age 80 years had a mean score on the MMSE that was three points less than women in the same age group. Logistic regression analyses revealed a trend with increasing age and decreasing educational status for receiving a score at or below 23 points, and men compared to women exhibited a 3.7-fold increased odds to score at or below this cutoff, even when scores were adjusted for age and education (OR = 3.7; 95% CI, 1.3–10.2).

After age– gender adjustment in our logistic models, PD patients did not differ with respect to a reported history of comorbid major medical conditions by PD subtype, except for possibly a higher odds of cancer reported by akinetic patients (OR = 2.6; 95%CI, 0.91–7.34), and a higher odds that female patients suffered from a thyroid condition (OR = 5.1; 95%CI, 1.7–15), yet no pronounced gender differences were seen for any of the other major medical conditions.

More female than male patients reported that both first-degree relatives and first- or second-degree relatives suffered from PD (Table 6; for female patients reporting a positive family history, age-adjusted OR = 3.3; 95% CI, 1.3– 8.3). There was no difference in reports of family history of PD between PD subtypes. However, patients under 70 years of age at diagnosis had a fourfold higher odds of having a first- or second-degree relative with PD compared to those diagnosed at on older age (age-gender–adjusted OR = 4.1; 95% CI, 1.63–10.2). Tremor-dominant patients had twice the odds of a positive family history for ET in comparison to the akinetic subtype (age-gender–adjusted OR = 2.1; 95% CI, 0.84 –5.4). PD patients less than 60 years of age reported few relatives affected by ET. When comparing across PD subtypes, akinetic–rigid patients had the highest odds of reporting a positive family history for AD (age-gender–adjusted OR = 2.3; 95% CI, 0.85– 6.7), but the confidence interval included the null value. Of interest, none of the 25 PD patients diagnosed at age 80 or older with PD reported a family history of AD.

DISCUSSION

The majority of our patients were men, Caucasian, and between 60 and 79 years of age, concurrent with findings from numerous epidemiological studies reporting a steep increase in PD incidence after 60 years of age[5,6,19] and generally a higher rate of disease in men.[2,4– 6,8] The majority of our patients, both men and women, were characterized as akinetic–rigid or tremor-dominant, whereas only a minority fell into the mixed category. The frequency of the tremor-dominant (39%) and akinetic–rigid (49%) types is roughly similar to the frequency of the tremor-dominant subtype (29%) and the postural instability and gait difficulty– dominant subtypes (55%) found in the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) study of new-onset patients.[13] The subtyping method we used in our study is most similar to methods used by Schiess and colleagues[12] and Korchounov and associates.[14] In contrast to our findings, Schiess and coworkers reported roughly equal distributions of the three subtypes in their population. The most likely explanation for the difference between our findings and those o Schiess' group is the inclusion of prevalent patients in their study who had been diagnosed with PD for a longer period of time (mean disease duration, approximately 9 years[12]). The study by Korchounov and colleagues[14] classified a comparable percentage of patients into mixed and akinetic–rigid subtypes (36% and 38%) and fewer patients as tremor-dominant (26%). However, all of these patients were younger than 74 years of age and reported to have suffered from PD symptoms for a longer duration (3– 6 years). It has been our clinical experience that PD patients may show prominent characteristics of tremor versus akinesia and rigidity in the initial stages of the disease, whereas as the disease progresses, other clinical signs may become apparent, but systematic longitudinal studies documenting progression and emergence of different motoric symptoms/signs are lacking.

Older patients in our study were somewhat more likely to be subtyped as akinetic–rigid, whereas younger patients were more frequently tremor-dominant. The akinetic–rigid subtype has been associated previously with a more malignant course compared to the tremor-dominant subtype.[20] Patients who are older at the time of PD onset have been shown to have a more rapid disease progression in comparison to patients with PD onset at younger ages.[21] Although our data seems to suggest that the reason for older patients progressing

more quickly might be that they more often suffer from the akinetic–rigid subtype from onset, we would need to follow up patients over time and compare the progression in subtypes within age groups to discern whether the rate of progression is determined by age at onset or the subtype.

Although patients included in this study were by definition in the "early stages" of PD (i.e., identified 1–3 years after a first diagnosis of PD was made by a physician) when gait and postural stability problems are not typically especially problematic,[22] a majority (87%) had already developed difficulty with gait. However, most of our subjects exhibited only minimal deficit of gait (70% were rated as "mildly impaired" in this UPDRS category). Deficits in stability and gait were somewhat more frequent in the oldest age groups; this finding concurs with that of Nagayama and associates[23] and Diederich and coworkers[21] who evaluated the initial symptoms in PD patients of advanced age. Although resting tremor is often thought of as the clinical "hallmark" of PD, it only occurred in our study in approximately half of the patients, whereas rigidity and bradykinesia were more frequent. The prevalence study by Zhang and colleagues[24] of PD in patients 55 years or older (median age of onset, 68.5 years) in Greater Beijing, China, similarly described that the initial sign of PD was resting tremor in only 62% of patients. In general, studies describing the frequency of tremor in the early stages of PD are lacking; this deficiency in the literature may contribute to the common misconception among general practitioners as well as patients that tremor is essential to arrive at a diagnosis of PD. The presence of tremor was slightly more frequent in our younger patients (< age 60 years) and in patients who were over 80 years of age at diagnosis. Another study evaluating the initial symptoms of PD patients reported that patients under 64 years of age had the highest frequency of tremor (70.6%) and a decreasing trend with age was seen (age 65–74 years, 41%; > age 75 years, 36%).[23]

A higher percentage of akinetic/rigid patients were classified as Hoehn and Yahr Stage 2 or higher in comparison to the tremor-dominant group. This finding is in agreement with the notion that akinetic–rigid patients may have a more malignant disease course. It is also possible that these patients were diagnosed later in comparison to tremor– dominant patients and, thus, were further along in their disease course when we evaluated them. In our study, women and men did not appreciably differ in Hoehn and Yahr scores. In contrast, Lyons and associates[25] found that women with PD had milder motoric symptoms in comparison to men. However, because these motor differences were found only in patients who had PD for more than 5 years, this finding may suggest a slower progression of disease in women. We hope to be able to examine this hypothesis through continued follow-up of our patients over time.

Patients under 60 years of age were less likely to be treated with L-dopa but more likely to be given dopamine agonists, suggesting that treating physicians followed standard practice guidelines in these rural counties,[26] i.e., treating early PD in younger patients with medication alternatives to L-dopa such as dopamine agonists in an attempt to minimize the development of motor fluctuations such as dyskinesias for which this age group has been found to be at higher risk.[27,28] There appear to be multiple reasons for 19% of our patients not being on PD medications, including (1) many of these patients having mild symptoms based on relatively low Hoehn and Yahr Scale scores, (2) inability to pay for medications, (3) not being treated by a neurologist, and (4) regional physicians' management choices in the treatment of PD patients. It is quite common for neurologists and other physicians to refrain from treating PD patients in the early stages of disease. However, this practice may prove to have implications in terms of symptom progression, as recent studies have demonstrated that treatment with dopamine agonists delays the onset of motor fluctuations[29] and early L-dopa therapy results in improved clinical scores.[30]

The cited frequency for depression in PD patients in the literature varies between 3% and 70%, depending on the method used to assess depression.[31] In our study, mean GDS scores did not show appreciable differences between gender, age group, and PD subtype. In contrast, Starkstein and coworkers[32] reported a higher frequency of depression (according to Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition diagnostic criteria and the Hamilton Depression Scale) for the akinetic–rigid subtype (disease duration, 6.6 years; prevalence of depression, 38%) compared to patients with "classic" PD (defined as presence of tremor plus rigidity and/or bradykinesia; disease duration, 4.9 years; prevalence of depression, 15%). Differences in comorbid depression depending on age of onset of PD have also been reported such that early-onset (< 55 years of age) patients suffered from depression (assessed by Hamilton Depression Scale and Present State Examination) twice as often as late-onset (> 55 years of age) patients.[33] This difference remained significant when the patients were matched for duration of disease (mean duration for early-onset group, 10.8 years; mean duration for late-onset group, 10.4 years). The difference in findings between our study and these other studies may be because previous studies only evaluated patients who had already suffered from PD for a prolonged period. Variations in the rate of depression according to PD subtype, however, may emerge several years after diagnosis of PD. In our study, 21 (13%) PD patients scored seven points or more on the GDS, whereas 23% had a history of taking antidepressant medication mostly in the recent past. Thus, we observed a relatively high rate of depression considering all patients were evaluated during the early years of the disease, but it would be interesting to follow our patients over time and document the occurrence of comorbid depression in relation to progression of motoric symptoms.

Our findings of 8.6% of patients reporting a family history of PD in a first-degree relative and 17.3% of patients in a first- or second-degree relative lie within the range reported in other studies.[34–36] We did not find differences for PD family history by subtype, whereas Korchounov and coworkers[14] reported increased family history of PD in patients compared to in-laws and friends for those falling into the tremor-dominant subtype and the akinetic–rigid subtype of "earlier onset" (< 60 years of age). We found that women reported a family history of PD more often. There are several possible explanations to account for this result: (1) women being more aware of diseases in relatives in comparison to men, (2) women over-reporting disease, and (3) actual higher rates of family history of PD among female patients. Several previous studies found no difference in the accuracy of men and women in reporting family history of PD[37] as well as other medical conditions such as cancer,[38] heart disease, diabetes, and asthma.[39] Furthermore, arguing against a reporting bias by women would be that the female patients in our study did not report a higher rate of family history of ET. We did not find other descriptions of an increased family history of PD reported by female patients in the literature. Our patients who were younger than 69 years at diagnosis had a slightly higher frequency of family history of PD. Few (only 11 of 162) patients were diagnosed with PD at <50 years of age. Only 1 patient reported a first-degree relative suffering from PD, whereas a larger number (8 or 25%) reported second-degree relatives with the disease.

Even after age- and gender-adjustment, tremor-dominant patients had the highest percentage of a family history of ET. PD patients have been reported previously as having a higher frequency of family history of ET in comparison to non-PD patients (15–23% of PD patients in comparison to 5 to 6% of control subjects),[36,40,41] which has led to the hypothesis that ET and PD may share a common etiological basis.[42] Our data suggest that the tremor-dominant subtype may be especially likely to share similar underlying genetic mechanisms.

Our data suggested a 2.3-fold increased risk for AD among the akinetic–rigid subtype compared to the tremor-dominant subtype, even after age-gender adjustment. Levy and

colleagues recently published data that did not show an increased risk of AD in first-degree relatives of either the postural instability gait disorder or tremor-dominant subtypes of PD in comparison to controls.[43] In the community-based study by Hofman and associates,[44] AD patients were approximately three times (7%) as likely to have a first-degree relative with PD, in comparison to non-AD affected controls (2.5%). The literature contains many references to clinical and pathological similarities between PD and AD: clinical associations have been found between PD and AD, and pathology studies have demonstrated similar types of findings in demented PD and in AD patients.[45,46] Furthermore, because a significant percentage of patients have clinical and pathological features of both AD and PD, the boundaries of both diseases remain unclear; and in instances of comorbidity; it has been suggested that the pathological cascades of the two diseases may overlap.[47]

Our study has some limitations. Recruitment or PD diagnosis in rural areas may have been hampered by lack of transportation. Although we offered to conduct home visits and paid for transportation, infrequent contact of patients with medical providers may have led to under-diagnosis in certain geographic areas. However, we have no reason to believe that PD patients who were diagnosed by a local provider and willing to participate differed from nonparticipants in a manner that resulted in selection bias with respect to PD subtypes. Patients were typically off their PD medications for at least 12 hours, which is the standard length of time used for practical and ethical reasons. The PD medications clearly can have longer half-lives than 12 hours. Therefore, it is feasible that certain clinical signs were masked during examination due to the medications continuing to have an effect. However, it has been our experience that even when off medications for this relatively short duration of time, the predominant motoric deficit (i.e., tremor vs. rigidity vs. bradykinesia) the majority of patients display is one which most troubled the patient before initiation of medication treatment. Accordingly, we believe that our classification was not greatly affected by medication use. Finally, the classification of subtypes by means of the ratio of tremor to akinesia–rigidity symptoms may seem arbitrary. Thus, we conducted various sensitivity analyses, which included choosing different cut-points than suggested by Schiess and associates and using means for both tremor and akinesia symptoms, or relying on the means for all items used by Korchounov and coworkers[14] We found that this strategy would increase the size of our mixed subtype to 32 patients (18%), mostly by reassigning tremor-dominant patients. The scores and ratios were all highly correlated no matter what method we chose, and none of the family history results we presented were affected.

Conclusions

This study represents the most extensive phenotypic description of U.S. patients recently diagnosed with PD who were recruited in a population-based manner. The general demographics and many of the clinical features of our population appear to be similar to those reported in previous population-based and clinical studies. The neurologists in the Central Californian counties studied had a high rate of appropriately diagnosing PD. Our population displayed phenotypic variation in terms of the predominance of certain neurological signs on examination, with the akinetic–rigid type already appearing to have worse motoric function in comparison to the other subtypes at this early stage of disease. Furthermore, the association we found between an increased family history of ET in tremor-dominant PD and AD in akinetic–rigid PD is suggestive of similar underlying genetic etiologies and possibly pathological processes between PD and these other neurological disorders. It is our intention to follow up these patients over the course of several years and assess the way in which clinical characteristics evolve. In addition, we plan to examine how genetics and environment may interplay with the development and progression of disease. Through documentation of the clinical characteristics at baseline and subsequently following these patients over time, we believe valuable information will be derived regarding the

prognostic indication of early symptoms/signs and shed light on phenotype/genotype associations and ultimately may provide clues to a better understanding of the underlying etiology of PD.

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TABLE 1

Demographic characteristics of Parkinson's disease patients

	Possible PD			Probable PD		
	N	**Males**	**Females**	**N**	**Males**	**Females**
Total	162	92 (56.8)	70 (43.2)	31	19 (61.3)	12 (38.7)
Age at diagnosis (yr)						
<60	37	22 (59.5)	15 (40.5)	6	3 (50.0)	3 (50.0)
60–69	39	27 (69.2)	12 (30.8)	7	4 (57.1)	3 (42.9)
70–79	69	32 (46.4)	37 (53.6)	13	8 (61.5)	5 (38.5)
>80	17	11 (64.7)	6 (35.3)	5	4 (80.0)	1 (20.0)
Race/ethnicity						
Caucasian	137	75 (54.7)	62 (45.3)	26	16 (60.0)	10 (40.0)
Hispanic/Latino	15	11 (73.3)	4 (26.7)	3	1 (33.30)	2 (66.7)
Asian	1	0 (0)	1 (100)	0	0 (0)	0 (0)
Native American	9	6 (66.7)	3 (33.3)	1	1 (100)	0 (0)
African–American	0	0 (0)	0 (0)	1	0 (0)	1 (100)

Values are expressed as n (%), unless otherwise indicated.

PD, Parkinson's disease.

TABLE 2

Parkinson's disease subtypes by sex and age group

	N	Akinetic-rigid	Mixed	Tremor-dominant
Sex				
Males	92	46 (50.0)	10 (10.9)	36 (39.1)
Females	70	33 (47.1)	9 (12.8)	28 (40.0)
Age at exam (yr)				
<60	28	10 (35.7)	3 (10.7)	15 (53.6)
60–69	40	19 (47.5)	3 (7.5)	18 (45.0)
70–79	69	39 (56.5)	8 (11.6)	22 (31.9)
>80	25	11 (44.0)	5 (20.0)	9 (36.0)
Total	162	79 (48.8)	19 (11.7)	64 (39.5)

Values are expressed as n (%), unless otherwise indicated.

TABLE 3

Frequency of UPDRS Motor symptoms by sex and age group

Age at exam (yr)	N	Speech (UPDRS 18)	Tremor (UPDRS 21)	Rigidity (UPDRS 22)	Bradykinesia (UPDRS 23–27, 31)	Posture (UPDRS 28)	Gait (UPDRS 29)	Postural Instability (UPDRS 30)
<60	28	12 (42.9)	16 (57.1)	28 (100)	26 (92.9)	18 (64.3)	24 (85.7)	9 (32.1)
60–69	40	26 (65.0)	18 (45.0)	37 (92.5)	38 (95.0)	27 (67.5)	35 (87.5)	8 (20.0)
70–79	69	41 (59.3)	28 (40.6)	63 (91.3)	67 (97.1)	59 (85.5)	59 (85.5)	32 (46.4)
>80	25	18 (72.0)	13 (52.0)	21 (84.0)	24 (96.0)	21 (84.0)	23 (92.0)	17 (68.0)
Total	162	97 (59.9)	75 (46.3)	149 (92.0)	155 (95.7)	125 (77.2)	141 (87.0)	66 (40.7)

Values are expressed as n (%), unless otherwise indicated.

UPDRS, Unified Parkinson's Disease Rating Scale.

TABLE 4

Modified Hoehn and Yahr staging scores

	N	Stage 1	Stage 1.5	Stage 2	Stage 2.5	Stage 3	Stage 4	Stage 5
PD subtype								
Akinetic-rigid	78	15 (19.2)	2 (2.6)	26 (33.3)	13 (16.7)	20 (25.6)	0 (0)	2 (2.6)
Mixed	19	4 (21.1)	1 (5.3)	9 (47.4)	2 (10.5)	3 (15.8)	0 (0)	0 (0)
Tremor-dominant	56	17 (30.4)	1 (1.8)	18 (31.2)	8 (14.3)	11 (19.6)	1 (1.8)	0 (0)
Age at exam (yr)								
<60	24	4 (16.7)	2 (8.3)	10 (41.7)	3 (12.5)	5 (20.8)	0 (0)	0 (0)
60–69	38	14 (36.8)	1 (2.6)	14 (36.8)	4 (10.5)	4 (10.5)	1 (2.6)	0 (0)
70–79	68	15 (22.1)	1 (1.5)	22 (32.4)	11 (16.2)	18 (26.5)	0 (0)	1 (1.5)
≥80	23	3 (13.0)	0 (0)	7 (30.4)	5 (21.7)	7 (30.4)	0 (0)	1 (4.4)
Total	153[a]	36 (23.5)	4 (2.6)	53 (34.6)	23 (15.0)	34 (22.2)	1 (0.7)	2 (1.3)

Values are expressed as n (%), unless otherwise indicated.

[a]Modified Hoehn and Yahr Scale stage data are missing for 9 participants.

PD, Parkinson's disease.

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TABLE 5

Parkinson's disease medication usage patterns

	N	Carbidopa/levodopa (Sinemet)	Dopamine agonists*	COMT inhibitors**
Men				
PD subtype				
Akinetic-rigid	46	23 (50.0)	20 (43.5)	4 (8.7)
Mixed	10	4 (40.0)	3 (30.0)	2 (20.0)
Tremor-dominant	36	8 (22.2)	20 (55.6)	1 (2.8)
Age at exam (yr)				
<60	19	3 (15.8)	13 (68.4)	2 (10.5)
60–69	27	11 (40.7)	14 (51.9)	2 (7.4)
70–79	32	16 (50.0)	13 (40.6)	2 (6.3)
≥80	14	5 (35.7)	3 (21.4)	1 (7.1)
Total	92	35 (38.0)	43 (46.7)	7 (7.6)
Women				
PD subtype				
Akinetic-rigid	33	3 (9.1)	16 (47.1)	2 (6.1)
Mixed	9	6 (66.7)	3 (33.3)	0 (0)
Tremor-dominant	28	11 (39.3)	9 (32.1)	2 (7.1)
Age at exam (yr)				
<60	9	2 (22.2)	8 (88.9)	1 (11.1)
60–69	13	4 (30.8)	4 (30.8)	0 (0)
70–79	37	10 (27.0)	13 (35.1)	1 (2.7)
≥80	11	4 (36.4)	3 (27.3)	2 (18.2)
Total	70	20 (28.6)	28 (40.0)	4 (5.7)
Total (M and F)	162	55 (34.0)	71 (43.8)	11 (6.8)

Values are expressed as n (%), unless otherwise indicated.

*Mirapex, Requip, Permax, or Parlodel.

**Comtan and Tasmar.

PD, Parkinson's disease; COMT, catechol-*O*-methyltransferase.

TABLE 6

Individuals with family history of Parkinson's disease, essential tremor, and Alzheimer's disease in first-and second-degree relatives

		Parkinson's disease		Essential tremor		Alzheimer's disease	
	N	1st degree	1st or 2nd degree	1st degree	1st or 2nd degree	1st degree	1st or 2nd degree
Sex							
Male	92	4 (4.4)	11 (12.0)	6 (6.5)	14 (15.2)	7 (7.6)	11 (12.0)
Female	70	10 (14.3)	17 (24.3)	6 (8.6)	11 (15.7)	9 (12.9)	12 (17.1)
PD subtype							
Akinetic-rigid	79	7 (8.9)	13 (16.5)	3 (3.8)	9 (11.4)	10 (12.7)	15 (19.0)
Mixed	19	2 (10.5)	3 (15.8)	2 (10.5)	2 (10.5)	2 (10.5)	3 (15.8)
Tremor-dominant	64	5 (7.8)	12 (18.8)	7 (10.9)	14 (21.9)	4 (6.3)	5 (7.8)
Age at exam (yr)							
<60	28	1 (3.6)	8 (25.6)	0 (0)	3 (10.7)	2 (7.1)	5 (17.9)
60–69	40	6 (15.0)	10 (25.0)	3 (7.5)	9 (36.0)	5 (12.5)	8 (20.0)
70–79	69	4 (5.8)	6 (8.7)	6 (8.7)	8 (32.0)	9 (13.0)	10 (14.5)
≥80	25	3 (12.0)	4 (16.0)	3 (12.0)	5 (20.0)	0 (0)	0 (0)
Total	162	14 (8.6)	28 (17.3)	12 (7.4)	25 (15.4)	16 (9.9)	23 (14.2)

Values are expressed as n (%), unless otherwise indicated.

PD, Parkinson's disease.