Movement Disorders
CLINICAL PRACTICE

BRIEF REPORT

Family History in Parkinson's Disease: A National Cross-Sectional Study

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Abstract: Background: Family history of Parkinson's disease (PD) is a common finding in PD patients. However, a few studies have systematically examined this aspect.

Objectives: We investigated the family history of PD patients, comparing demographic and clinical features between familial PD (fPD) and sporadic PD (sPD).

Methods: A cross-sectional study enrolling 2035 PD patients was conducted in 28 Italian centers. Clinical data and family history up to the third degree of kinship were collected.

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Keywords: familial and sporadic Parkinson's disease, family history, hyposmia, cognitive impairment, depression, bipolar disorder.

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Results: Family history of PD was determined in 21.9% of patients. fPD patients had earlier age at onset than sporadic patients. No relevant differences in the prevalence of motor and nonmotor symptoms were detected. Family history of mood disorders resulted more prevalently in the fPD group.

Conclusions: fPD was found to recur more frequently than previously reported. Family history collection beyond the core family is essential to discover disease clusters and identify novel risk factors for PD.

Parkinson's disease (PD) is a neurodegenerative disorder clinically characterized by the presence of bradykinesia, variably associated with resting tremor, muscle rigidity, and postural instability. Concerning its controversial etiopathology, both genetic and environmental factors are likely involved.[1–3]

Positive family history for PD is an established risk factor for the development of the disease, especially in first-degree relatives, whose risk for the disease is estimated to increase by 2- to 3-fold.[4,5] Previous studies reported familial recurrence of PD in 5% to 15% of patients.[6,7]

This study aimed to analyze the family history of PD patients up to the third degree of kinship, assessing the frequency of familial forms of PD and comparing demographic and clinical features between familial (fPD) and sporadic (sPD) patients. The prevalence of other neurological and psychiatric disorders across family members was also assessed.

Patients and Methods

This is a cross-sectional study performed in 28 Parkinson's disease and movement disorders centers, located in 14 Italian regions.

Patients were consecutively recruited from outpatient clinics during a 30-month period, from April 1, 2020, to November 30, 2021.

The following inclusion criteria were applied to establish patient eligibility:

a. Confirmed diagnosis of PD made by a movement disorder specialist, according to the Movement Disorder Society clinical diagnostic criteria[4]
b. Signed informed consent to participate in the study
c. Age over 18 years at the time of assessment

Exclusion criteria were defined as follows:

a. Secondary or atypical parkinsonism
b. Lack of sufficiently comprehensive biographical, clinical and anamnestic information

All data were entered into an electronic database. For each patient, family history for PD, essential tremor (ET), cognitive impairment, and major depressive and bipolar disorders was assessed up to the third degree of kinship using a structured family history interview.

The occurrence of one of the aforementioned conditions in PD family members was classified as follows:

- Certain, if the disease was diagnosed by a neurologist or a psychiatrist for what concerns movement disorders and psychiatric conditions/mood disorders, respectively
- Possible, if the disease was reported by patients or caregivers without formal assessment by a physician
- Negative, if the disease never occurred in the family
- Unknown, if data on family history were incomplete/missing (eg, in the case of adoption, early death, abandoned)

Clinical and genetic data were obtained through neurological examination and local databases. Descriptive statistic was employed to characterize the population demographics. Categorical variables have been reported as count (percentage) and continuous variables as mean (standard deviation). Statistical comparisons between groups were performed using Fisher's exact test for categorical variables and Wilcoxon 2-sample test for continuous variables. Statistical significance was set at the $\alpha = 0.05$ level, 2 sided. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

The entire study population was considered for demographic and epidemiological analyses. Only patients with certain (fPD) or negative (sPD) PD family history were included in comparison analyses.

Results

Family History for PD and Other Neuropsychiatric Disorders in PD Patients

According to inclusion/exclusion criteria, 2035 PD patients were included in the study.

A male predominance was observed, with a male-to-female ratio of 1.5:1.0. The mean age at evaluation was 68.9 ± 10.6 years, the mean age at onset of motor symptoms was 60.2 ± 11.5 years, and the average disease duration was 8.7 ± 5.9 years.

A family history of any degree for PD was reported by 34.5% of PD patients (n = 703, certain plus possible). However, a formal diagnosis of PD could be demonstrated in the relatives of 21.9% of cases (n = 446, certain) (Fig. 1).

Considering PD patients with certain or possible family history for PD, 67.9% (477/703) reported at least 1 first-degree affected relative, whereas 32.1% (226/703) described only second- or third-degree affected family members.

As concerns other neurological and psychiatric disorders, 11.9% (n = 243) of PD patients reported certain family history for cognitive

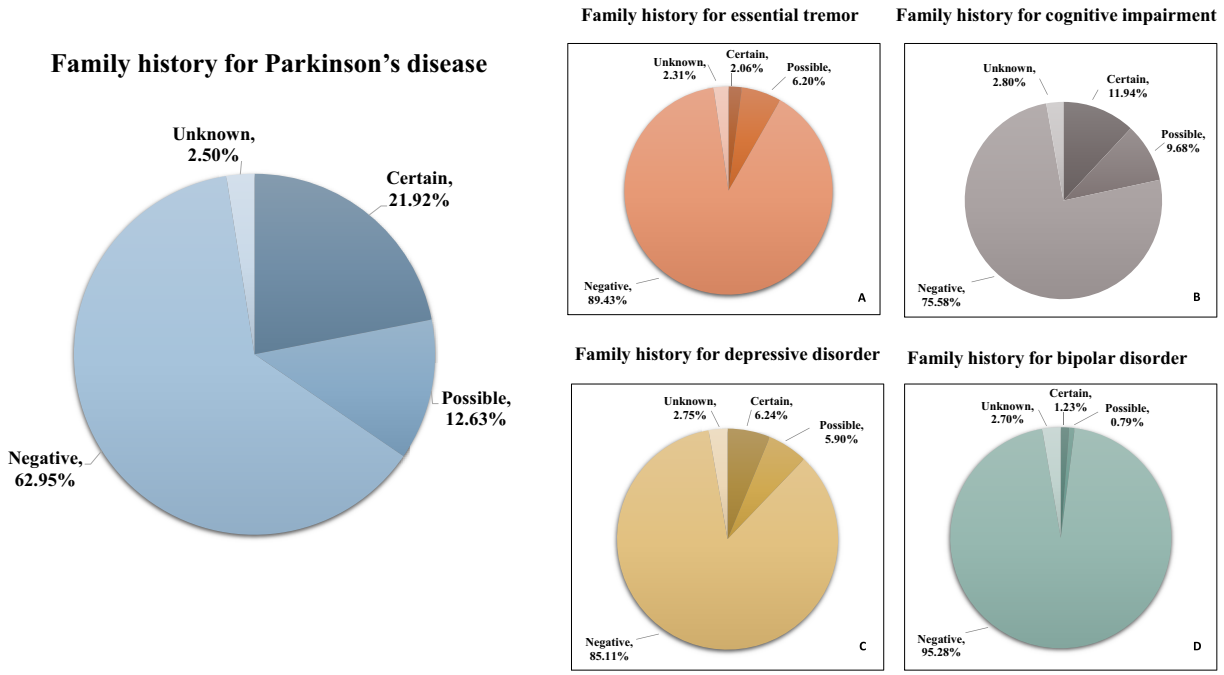

FIG. 1. Pie charts showing the diseases (PD, ET, Cognitive Impairment, Depressive Disorder, Bipolar Disorder) for which the family history was investigated and the percentages of certain, possible, negative, and unknown family history.

impairment, 2% (n = 42) for ET, and 6.2% (n = 127) and 1.2% (n = 25) for depression and bipolar disorders, respectively (Fig. 1A–D). The inclusion of possible cases in the estimation of prevalence significantly increased numbers as follows: cognitive impairment = 21.6% (n = 440), ET = 8.2% (n = 168), depression = 12.1% (n = 247), and bipolar disorder = 2% (n = 41).

Comparison between fPD and sPD

No differences in mean age and sex distribution between fPD (n = 446) and sPD (n = 1281) groups were observed. The mean age at onset was significantly lower in fPD patients (58.5 ± 11.5 years) than in sPD (60.8 ± 11.5 years) ($P = 0.0001$), and mean disease duration was longer in the fPD group (9.6 years) than in the sPD group (8.4 years) ($P = 0.0002$). No relevant difference between the 2 groups in the modified Hoehn and Yahr Staging Scale scores corrected for disease duration was observed.

The distribution of motor and nonmotor symptoms between fPD and sPD was similar, except for hyposmia that resulted more frequently in the fPD group (Table 1).

Family history of depressive disorder (9.8% vs. 5.7%, $P = 0.0058$) was more common in fPD. A similar but not significant trend was observed for ET (3.7% vs. 2.0%, $P = 0.0647$), whereas no differences were observed in the recurrence of cognitive and bipolar disorders.

Genetics

Genetic testing was performed in 21.8% (443/2035) of the patients. In all cases a minimal gene set (ie, *SNCA*, *LRRK2*, *GBA1*, *PRKN*, and *PINK1*, including relevant dosage assays) was analyzed.

Considering the 372 subjects tested with certain positive or negative family history, a positive genetic result was more frequent in fPD (55/151, 36.4%) than in sPD (57/221, 25.8%) ($P = 0.0295$). The prevalence of pathogenic variants in the most common PD genes (*GBA1*, *LRRK2*, and *PRKN*) did not differ between sPD and fPD patients (Table S1). Most of the enrolled patients were not genetically tested, thus precluding further analyses and possibly enriching the rate of positive results by having selected more likely genetic cases (eg, due to family history, clinical characteristics or geographical origin).

Discussion

The frequency of family history of PD is known to be higher among PD cases than the general population.[5,6] Previous studies reported that about 10% to 15% of PD patients have at least 1 affected relative.[7,8] In this study, more than one-third of PD patients (34.5%) presented a positive family history for PD (21.9% when considering only certain cases, thus eliminating the limitation due to the anamnestic report of possible cases). The

TABLE 1 *Comparison of clinical characteristics between patients with fPD and sPD*

	fPD (n = 446)	sPD (n = 1281)	Statistical significance
Motor symptoms			
Rest tremor, % (n)	68.6 (306)	67.2 (861)	$P = 0.5977$
Rigidity, % (n)	86.1 (384)	85.1 (1090)	$P = 0.6413$
Postural instability, % (n)	24.0 (107)	25.3 (324)	$P = 0.6116$
Freezing, % (n)	20.4 (91)	17.4 (223)	$P = 0.1755$
Dystonia, % (n)	12.6 (56)	11.0 (141)	$P = 0.3874$
Pisa syndrome, % (n)	7.6 (34)	8.1 (104)	$P = 0.8393$
Camptocormia, % (n)	21.8 (97)	22.2 (284)	$P = 0.8946$
Nonmotor symptoms			
Hyposmia, % (n)	42.6 (190)	35.4 (453)	***P = 0.0075***
Constipation, % (n)	53.4 (238)	49.6 (635)	$P = 0.1698$
Orthostatic hypotension, % (n)	16.1 (72)	17.1 (219)	$P = 0.6603$
Urinary symptoms, % (n)	41.3 (184)	39.0 (499)	$P = 0.3994$
Sialorrhoea, % (n)	15.9 (71)	13.5 (173)	$P = 0.2075$
Rem behavior disorder, % (n)	46.0 (205)	43.3 (555)	$P = 0.3467$
Depression, % (n)	31.6 (141)	31.2 (399)	$P = 0.8589$
Bipolar disorder, % (n)	0.9 (4)	0.6 (8)	$P = 0.5195$
Cognitive decline, % (n)	13.5 (60)	16.6 (212)	$P = 0.1314$
Psychosis, % (n)	8.5 (38)	10.2 (131)	$P = 0.3105$
Anxiety, % (n)	33.0 (147)	29.4 (377)	$P = 0.1692$
Pain, % (n)	23.8 (106)	19.8 (253)	$P = 0.0781$
Family history of neuropsychiatric disorders			
Essential tremor, % (n)	3.7 (15)	2.0 (24)	$P = 0.0647$
Cognitive impairment, % (n)	15.6 (61)	13.8 (160)	$P = 0.4027$
Depression, % (n)	9.8 (40)	5.7 (68)	***P = 0.0058***
Bipolar disorder, % (n)	1.4 (6)	1.3 (16)	$P = 0.8082$

Statistically significant differences are indicated in blue, whereas trends of clinical interest are highlighted in gray.
Abbreviations: fPD, familial Parkinson's disease; Rem, rapid eye movements; sPD, sporadic Parkinson's disease.

higher rate of positive family history encountered may suggest either a major role played by genetic factors in the Italian PD population or a possible underestimation in previous studies. A plausible explanation may be the limitation of data collection to first-degree relatives. Interestingly, a remarkable 32.1% of PD patients reported only second- or third-degree affected family members, which should prompt clinicians to investigate the family history more thoroughly.

As a matter of fact, given the incidence of PD in the general population, the presence of more than 1 family member affected may not be related to genetic factors.

In line with previous studies,[6,9,10] fPD exhibited younger age at onset. This observation could be due to a higher prevalence of genetic forms in fPD or to an earlier recognition of PD symptoms by patients with affected relatives.[11]

No major differences in motor phenotype between fPD and sPD were observed, confirming previous observations,[9,12] with a few exceptions.[10]

Among nonmotor features, hyposmia was more represented in the fPD group. A clear explanation of this finding is still elusive. The higher prevalence may be due to PD genetic risk factors predisposing also to PD-related hyposmia in familial cases.[13] However, confounding factors (eg, cigarette smoking, allergies, drugs) that were not collected in this study may also play a role.

We then investigated the occurrence of neurological and psychiatric features in relatives of PD patients. To this aim, we collected data on whether PD relatives had a diagnosis of disorders previously associated with PD (ie, ET, bipolar disorder, and depression) or presented clinical features (ie, tremor, cognitive

impairment, and mood disorders), which may occur in prodromal PD.

A certain diagnosis of ET was present in family members of 2% of the patients, whereas in 6.2% the diagnosis of ET was reported as possible. The remarkable difference between the certain and possible ET diagnoses is likely reflecting the uncertainty in categorizing tremor in terms of diagnosis and phenomenology. Indeed, the coexistence of PD and ET has been reported in PD patients, and ET was consistently found with a higher prevalence in family members of PD patients compared to those of controls.[14]

However, the relationship between ET and PD remains controversial, and most studies failed to find a significant connection.[15] These observations should prompt the collection of family history of ET in PD patients, encouraging further assessments and clinical studies to better understand these associations.

A diagnosis of cognitive impairment was reported from 12% (certain) to 21% (certain + possible) of PD families. This prevalence did not include relatives affected by PD dementia. A precise characterization of the cognitive disorders (Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, etc.) was often not retrievable due to missing anamnestic data. Such a prevalence of cognitive impairment in PD family members may be explained by shared molecular mechanisms between PD and other neurodegenerative disorders, as demonstrated by the presence of common genetic risk factors (ie, *GBA1*, *C9ORF72*, *MAPT*, *PSEN1*).[16–20]

Depression and anxiety were referred in 32% and 31% of PD patients, respectively (Table 1). This finding is higher compared to the reported prevalence of such symptoms in the Italian population (3%–6% and 2%–5%, respectively).[21,22] Notably, bipolar disorder, which has been proposed as a risk factor for PD, was quite rare in this cohort, occurring in 0.7% of patients.[23,24] Finally, a higher prevalence of mood disorders was observed in family members of fPD compared to sPD relatives. This observation may suggest a role of genetic factors in the predisposition of mood disorders, likely representing prodromal symptoms of PD.

In conclusion, PD patients have a higher prevalence of family members affected than previously reported, reaching up to one-third of cases after recording information on second- and third-degree relatives. This observation should stimulate further studies evaluating the risk of PD in family members to improve the counseling in PD patients and their families. Moreover, the identification of familial clusters will help to dissect the genetic and nongenetic contributions to the pathogenesis of PD and other neurodegenerative disorders.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique.

F.A.: 1A, 1B, 1C, 2A, 2B, 3A

G.C.: 2A, 2B, 2C

G.F., G.L., E.M., A.D.M.: 1C, 2A, 3B, 3B

A.D.F.: 1A, 2C, 3B

C.C., L.L., M.Z., A.R., F.S., P.D.M., N.T., A.A., A.A., M.C., L.A., R.M., F.D.B., T.B.M., M.C., A.R., R.C., G.P., A.F., A.C., N.T., E.M., G.C., L.M., C.C., E.C., R.C., R.E., P.B., M.P., C.S., V.F., C.L., M.C.M., M.P., C.L., O.D., R.D.G., A.P., A.P., A.L., A.I., M.C.S., G.C., A.B., C.S., G.D.L., A.B., P.N., F.T., E.C., P.V.M., S.T., A.T., R.D.M., S.A., M.T., I.D., S.O., P.T., F.D.B.; A.D'A.; F.V., F.C., G.T., V.F., M.A.V., L.C., S.G., G.D.N., D.V., M.Z., E.M.V., F.B.: 1C, 3B

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Disclosures

Ethical Compliance Statement: The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Milan (Comitato Etico Milano Area 2, parere 1106_2019). Written informed consent was obtained for each patient participating in this work. All authors have read and complied with the journal's ethical publication guidelines. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Distribution of GBA1, LRRK2 and PARK2 mutations in fPD and sPD with positive results in genetics analysis.