Familial Parkinson's Disease: A Clinical Genetic Analysis

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ABSTRACT: ***Objective:*** To study the frequency, clinical features and clinical genetics of familial Parkinson's disease (PD). ***Methods:*** Family history for PD and tremors was studied in 100 consecutive PD cases. Spouses served as controls. Clinical features were compared between personally verified familial and sporadic PD cases, from the same consecutive clinical series. Clinical genetic analysis was performed in a larger group of non-consecutive multicase PD families. ***Results:*** Family history for PD was positive in 24% of consecutive PD cases and in 6% of spouse controls ($p < 0.001$). When family history for isolated tremor is also considered, the number of positive cases rises to 43% compared with 9% in controls ($p < 0.001$). Nine of the consecutive cases had at least one living affected relative, for a total of 20 familial PD cases. These familial cases showed an earlier onset age when compared with sporadic ones from the same consecutive series. Within 22 non-consecutive PD families with at least two living and personally examined PD cases (total 52 PD cases), the crude segregation ratios were similar for parents and siblings and the lifetime cumulative risks approached 0.4 in siblings and tended to be comparable, but at later ages, in parents. Ancestral relatives were all unilaterally distributed. In some families, anticipation of onset age in new generations was observed. ***Conclusions:*** The frequency of positive family history for PD and for PD and tremor is higher among PD cases than controls. Familial and sporadic PD only differ in onset age. The clinical genetic analyses support autosomal dominant inheritance with strongly age-related penetrance as most likely in familial PD.

RÉSUMÉ: Maladie de Parkinson familiale: analyse génétique clinique. ***Objectif:*** Étudier la fréquence, les manifestations cliniques et la génétique clinique de la maladie de Parkinson familiale (MP). ***Méthodes:*** Nous avons étudié l'histoire familiale quant à la MP et au tremblement chez 100 cas consécutifs de MP. Les conjoints ont servi de contrôles. Nous avons comparé les manifestations cliniques entre les cas familiaux et sporadiques de MP confirmés personnellement, dans cette même série de cas. Nous avons procédé à une analyse génétique clinique chez un groupe plus considérable de familles comprenant plusieurs cas de MP non consécutifs. ***Résultats:*** L'histoire familiale était positive chez 24% des cas consécutifs de MP et chez 6% des conjoints servant de contrôles ($p < 0.001$). Quand nous tenons également compte d'une histoire familiale de tremblement, le nombre de cas positifs s'élève à 43% comparé à 9% chez les contrôles ($p < 0.001$). Neuf des cas consécutifs avaient au moins un membre vivant de sa famille qui était atteint, pour un total de 20 cas de MP familiale. Ces cas familiaux présentaient un âge de début plus précoce comparé aux cas sporadiques de la même série de cas consécutifs. Dans 22 familles de MP non consécutives comprenant au moins deux cas de MP vivants et examinés personnellement (pour un total de 52 cas de MP), le ratio de ségrégation brut était le même pour les parents et la fratrie, et le risque cumulatif à vie, qui était de près de 0.4 dans la fratrie, avait tendance à être comparable chez les parents, mais à un âge plus tardif. Les cas dans la parenté plus éloignée étaient toujours dans la même lignée, soit paternelle ou maternelle. Dans certaines familles, nous avons observé un phénomène d'anticipation quant à l'âge de début de la maladie dans les générations subséquentes. ***Conclusions:*** Une histoire familiale de MP et de MP et tremblement est plus fréquente parmi les cas de MP que parmi les contrôles. La seule différence entre les cas familiaux et sporadiques est l'âge de début de la maladie. Les analyses génétiques cliniques sont en faveur d'une hérédité autosomale dominante de la MP, avec une pénétrance fortement reliée à l'âge.

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The significance of genetic factors in the etiology of Parkinson's Disease (PD) has recently been re-evaluated.[1-2]

The methodology of classical clinical studies on PD twins, which seemed to exclude a genetic etiology, has been reappraised in the light of recent pathophysiological observations.[3] The interval which may lapse before a co-twin develops PD can be as long as 26 years.[2] Moreover, the concordance is higher if PET is used to detect the nigrostriatal disruption in co-twins,[4] or in asymptomatic relatives of PD patients.[5]

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Some large kindreds with autopsy-proven Lewy Body PD indicate an autosomal dominant transmission of PD.[6-9] In the largest such family, the penetrance approaches 100%, showing that PD can be provoked by a monogenic mechanism, in a classical Mendelian mode.[7] However, large kindreds like that are very rare. In the majority of smaller families with multiple PD cases it is difficult to distinguish between genetic and non-genetic etiologies; the familial occurrence of PD might be coincidental, or reflect exposure to shared environmental factor(s) or have mixed genetic-environmental basis.[1,2,10,11] In the few carefully performed studies on large numbers of PD multicase families, some suggested an autosomal dominant inheritance with reduced penetrance, while others favoured multigenic-multifactorial models (a number of genetic loci, each contributing to the total genetic risk, and additional non-genetic factors).[12-16]

A number of case-control studies performed with more rigorous methods than earlier ones, show that family history for PD is one of the strongest risk factors for the disease, but due to case ascertainment on the basis of history alone, they may be criticized.[17-19]

To overcome that we measured the frequency of positive family history for PD and tremors in a consecutive clinical series of 100 PD patients and their spouse controls (*Study 1*). We then examined all the relatives of the consecutive patients said to be affected by PD in order to verify the diagnosis and compare the clinical features of familial and sporadic PD cases (*Study 2*). Lastly, we collected a larger number of non-consecutive multicase PD families to perform a clinical genetic analysis (*Study 3*).

Methods

Study 1: comparison of 100 consecutive PD cases and their spouse controls.

During the period May-December 1993 we observed 100 consecutive PD patients at our clinic. The diagnosis of PD was made when at least two of the following: rest tremor, bradykinesia, muscular rigidity were present, and no cause of secondary parkinsonism was detected. Asymmetric onset, progressive disorder, improvement on l-dopa for at least 5 years and clinical course of at least 10 years were used as supportive evidence for the diagnosis of idiopathic Parkinson's disease.

These patients and their spouses, used as controls, were submitted to a detailed interview designed to obtain information on the presence of relatives affected by PD or tremors. None of the spouses, all of whom were personally examined, had PD symptoms or PD diagnosis. Their use as a control group minimizes the "awareness bias". In fact, as spouses of a PD patient, they are more aware of cases of PD in their own family than another control group might be. Co-informants were not used, except for a few PD cases with cognitive deterioration, whose family history was reconstructed with the aid of a relative other than the spouse.

Study 2: analysis of multicase PD families from the consecutive case series.

From this consecutive series, the patients who reported at least one living affected relative were further analysed, with the reconstruction of a detailed pedigree. For the deceased relatives presumed affected, the onset age was reconstructed on the basis of history. All the living relatives reported by the proband to be affected by PD were personally examined by one of us (V.B., E.F., M.D.M.). We also made an effort to examine those relatives who were alive and described as healthy. Some remaining relatives aged > 40 were asked on telephone about the presence of parkinsonian symptoms. The clinical features were compared between the familial and sporadic PD cases in this consecutive case series to exclude "interesting family" biasing effects.[20]

Comparisons between frequencies and averages used a χ^2 test with Yates' correction, Fisher exact test, and Student t-test, where appropriate.

Study 3: analysis of a larger group of non-consecutive multicase PD families.

Other multicase families seen by different neurologists were examined by us similarly and added to those from our consecutive case-series, to enlarge the pool of families for clinical genetic analysis.

Segregation ratios were calculated using the Weinberg proband method and assuming single incomplete ascertainment of families.[20] Briefly, the ratio between the affected and total number of siblings is calculated, excluding the probands. This is needed to correct the overestimate of the segregation ratios due to the "ascertainment bias" (the sibships with more affected members have a higher chance of being represented in hospital-based studies, thus causing a systematic excess of affected persons).[20] Standard errors of ratios were obtained using the formula $\sqrt{p(1-p)/n}$. Both the examined and unexamined (deceased) affected cases were included in this analysis.

To adjust for age-related incidence of PD, we applied the Kaplan-Meier survival analysis for an estimate of the cumulative lifetime risk of PD among siblings and parents of the probands.[21-23] Living or deceased individuals without PD were censored at the age of examination or age at death respectively. The probands were excluded. At each age, the cumulative risk is [1-(p)], where (p) is the cumulative disease-free survival.

This method was applied to the cohort of first degree relatives, parents and siblings, of the 100 consecutive cases, of the whole group of multicase families, and of monogeneration and multigeneration families separately. Differences in curves were tested for significance using the Mantel-Cox log rank chi-square test.[24]

Ancestral (excluding parents) relatives were also analysed according to the method of Slater et al.[25] This is a comparison of the pairs of ancestral affected relatives who are distributed unilaterally (on the paternal or maternal side) with those distributed bilaterally. Under a multigenic model, up to twice as many unilateral pairs as bilateral pairs are expected. A greater excess of unilateral pairs supports a monogenic model.

The age-at-onset and year-of-onset correlation in pairs of PD relatives was studied using the linear regression analysis.

Results

Study 1

In this consecutive series of 100 PD cases, there were 61 males and 39 females. The mean age was 68.04 ± 8.59 for the patients and 65.95 ± 9.41 for controls (p = 0.10). Both the patients and controls were Caucasian. The average number of family members (including parents, grandparents, siblings,

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uncles and first cousins) was 30.21 ± 16.65 for the patients and 30.69 ± 18.85 for the controls (p = 0.85).

The frequency of positive family history for PD and for PD and tremors was significantly higher among PD cases than spouse controls (Table 1).

Among consecutive cases with PD onset ≤ 50 and > 50 there were 35.3% and 20.7% respectively with positive family history for PD ($\chi^2 = 0.97$, p = 0.32).

Study 2

Among the 24 PD patients of the consecutive series, who report a positive family history for PD, there were 13 with at least one living relative said to be affected. In 3 cases the affected relative either refused to participate in the study or could not be contacted. In one other case the relative (a first cousin of the proband) was found at examination to have an isolated tremor of mixed rest and postural type in her right hand. This patient, then 65 years old, said she had had this tremor for one year. Since she might have either essential tremor or initial symptoms of PD, we decided to exclude this family from the analyses.

In the remaining 9 families a clinical diagnosis of PD was confirmed in at least one relative, making a total of 20 living and personally verified PD cases (9 probands and 11 secondary cases).

These familial cases showed an earlier onset than PD cases from the consecutive series with no family history of either PD or tremor. All other clinical features in familial and sporadic cases were similar (Table 2). We found 4 families with 1 generation, 3 with 2 generations, 1 with 3 generations and 1 with 4 generations containing PD cases.

Study 3

Another 13 (7 multigeneration and 6 monogeneration), non-consecutively ascertained families with at least two living PD cases were provided by other colleagues, and examined by us in a similar manner. These displayed no clinical differences when compared with the 9 multicase families from our consecutive patients. These two groups were therefore pooled to increase the number for analysis.

We had a total of 22 multicase PD families (10 monogeneration, 12 multigeneration) with 52 living affected members whose diagnosis was confirmed at examination by one of us (22 probands and 30 secondary cases). Within the secondary cases, 22 were among first degree relatives and 8 in more distant ones. Another 10 deceased members were reported to be affected by PD by history (2 first degree, 8 more distant). We observed 2 additional cases of isolated tremor in living relatives. As in a previous study,[15] no relatives said to be healthy were found to be affected.

Table 1: Frequencies of positive family histories for PD or tremor in 100 consecutively seen cases and controls.

	Family history for PD only		Family history for PD or tremor	
	Cases	Controls	Cases	Controls
Yes	24 (%)	6 (%)	43 (%)	9 (%)
No	76 (%)	94 (%)	57 (%)	91 (%)
Total	100	100	100	100
	$\chi^2 = 11.333$, p < 0.001		$\chi^2 = 28.300$, p < 0.001	
	Odds ratio = 4.95 95% c.i. = 2.05 - 11.94		Odds ratio = 7.63 95% c.i. = 3.67 - 15.79	

Table 2: Clinical features in familial and sporadic PD cases from our consecutive case series. Familial cases include 9 probands and their 11 living, personally examined, affected relatives. Sporadic consecutive cases are those with no family history of either PD or tremor.

		Familial (n.20)	Sporadic (n.57)
Sex:	Males	14	38
	Females	6	19
Mean age at examination		67.4 ± 8.4	69.4 ± 8.3
Mean age at onset		54.7 ± 11.8	60.9 ± 8.9*
Mean disease duration at examination		12.3 ± 8.4	8.5 ± 4.7**
Symptoms at onset:			
	Tremor	12	35
	Bradykinesia	8	16
	Unclear	0	6
Distribution of symptoms at onset:			
	Asymmetric	18	51
	Symmetric	1	5
	Unclear	1	1

* p = 0.016 ; ** p = 0.015 (Student t-test). All other differences are statistically not significant.

Clinical features. The clinical features of these 52 cases were as follows: 33 males, 19 females; mean age 64.3 ± 11.8 (SD); onset age 52.7 ± 12.6; disease duration 11.2 ± 7.2; symptoms at onset were tremor in 27, bradykinesia in 21, and unclear in 4 cases; onset was asymmetric in 41, symmetric in 7, unclear in 4 cases. We observed 10 families with 1 generation, 7 with 2 generations, 4 with 3 generations and 1 with 4 generations containing PD cases. In 8 families there were only sibs and in 2 only first cousins affected. Information on second degree relatives was incomplete in 7 of these 10 families (patients unable to recall or relatives had emigrated or lost contact).

Comparison between multi- and mono-generation families. A preponderance of men was observed within multigeneration family cases (Table 3). However, among the 23 affected males seen in multigeneration families, 10 cases were paternally and 12 maternally transmitted, pointing against X-linked and mitochondrial inheritance. Yet, all other clinical features were similar in multi- and mono-generation family patients (Table 3). Therefore, we conducted clinical genetic analyses including all the 22 families.

Pedigree and segregation analyses. The transmitting lineage by pedigree analysis (including healthy obligate carriers) was paternal in 10 cases, maternal in 14, both paternal and maternal in 1 case (due to consanguinity), and unknown in the remaining 27 cases. All the 10 paternally transmitted cases were males. Of the 14 maternally transmitted ones, 12 were males and 2 females (p = 0.49, Fisher exact test). The proband with both paternal and maternal transmission had a very early onset (age 28); his family has previously been described.[26]

There were 9 cases with one affected parent. All 4 cases with an affected father were males, whereas of the 5 cases with an

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Table 3: Clinical features in 10 monogeneration and 12 multigeneration PD families including clinically confirmed 52 PD relatives.

		Monogeneration cases (n.23)	Multigeneration cases (n.29)
Sex:	Males	10	23*
	Females	13	6
Mean age at examination		65.9 ± 10.5	63.1 ± 12.7
Mean age at onset		53.6 ± 12.2	52.0 ± 13.1
Mean disease duration at examination		11.5 ± 7.5	11.0 ± 7.1
Symptoms at onset:			
	Tremor	11	16
	Bradykinesia	10	11
	Unclear	2	2
Distribution of symptoms at onset:			
	Asymmetric	16	25
	Symmetric	4	3
	Unclear	3	1

* χ^2 with Yates' correction = 5.64, p = 0.018; all other differences are statistically not significant.

affected mother, 4 were males and 1 was female (p = 1, Fisher exact test).

For segregation analyses, one nuclear family was used in 16 of the 22 kindreds. Two and three nuclear families, excluding the secondary probands, were used from 3 and 1 multigeneration larger kindreds respectively.[20] Two nuclear families were also considered for each of the 2 kindreds containing only two affected first cousins, making a total of 29 nuclear families. The crude segregation ratios are shown in Table 4. There are no significant differences between parents and siblings of probands in the 22 families (χ^2 = 0.9, p = 0.34) and between non-proband siblings of the multi- and mono-generation families (χ^2 = 0.01, p = 0.92).

Cumulative lifetime PD risk estimates. The Kaplan-Meier lifetime cumulative risks for siblings of probands in the multi- and mono-generation families are almost superimposed (log rank χ^2 = 1.14, p = 0.286) (Figure 1). When the 22 families are considered together (Figure 2), the non-proband siblings show a lifetime risk of 0.37 ± 0.07 by age 75, whereas among the parents the risk is 0.16 ± 0.05 by age 74. This difference is significant (log rank χ^2 = 6.346, p = 0.012). Moreover, Figure 2 shows that the curve of cumulative risk for parents shows a delay of about 15 years but it draws closer to the curve of siblings in the oldest ages.

Kaplan-Meier analysis among the cohort of first degree relatives of the 100 consecutive cases of *Study 1* yielded lifetime cumulative risks of 0.058 ± 0.02 by age 79 for all non-proband siblings and 0.065 ± 0.02 by age 76 for their parents. The siblings of probands with an affected parent had a markedly increased risk (0.42 ± 0.2 by age 79, N = 3) (log rank χ^2 = 7.5, p = 0.006 versus all the non-proband siblings).

Monogenic/multigenic models. In the 22 multicase families, there were 14 ancestral affected relatives, all unilaterally distributed. According to Slater's method, they are combined in nine unilateral and no bilateral pairs; this preponderance differs statistically (p < 0.05) from the 2:1 ratio predicted by the multigenic model, and suggests a monogenic dominant inheritance.

Table 4: Crude Segregation Ratios.

	Aff./Total		Ratio ± SE
All Families	Parents	8/58	0.14 ± 0.05
	Siblings	26/125	0.21 ± 0.04
Multigeneration Families	Parents	8/34	0.24 ± 0.07
	Siblings	14/66	0.21 ± 0.05
Monogeneration Families	Siblings	12/59	0.20 ± 0.05

Onset age considerations. There is no intrafamilial correlation between the year of PD onset, when all the pairs of relatives are considered (r = –0.1, p = 0.618) or if only the sib/sib pairs are plotted (r = –0.38, p = 0.15) (data not shown). The age of PD onset instead shows a significant intrafamilial correlation (r = 0.475, p = 0.009), which is even stronger if only the sib/sib pairs are considered (r = 0.64, p = 0.004) (Figure 3). Moreover, the variance of onset age within single generations was significantly lower than within multiple generations (t = 2.174, p = 0.042), and it was found that onset in offspring in 8 out of 9 pairs of parent-offspring type (including 4 unexamined affected parents whose onset age was accurately referred by relatives), occurred at a younger age.

Discussion

Significance of the familial aggregation in PD

In recent case-control studies, conducted utilizing rigorous epidemiological approach and multivariate analysis, family history for PD has emerged as one of the strongest risk factors.[17-19] In the largest of these studies, Semchuk et al.[19] found that 22.7% of their 130 cases had a positive family history, compared with 6.3 % of 260 controls; the crude odds ratio was 5.76 (confidence intervals 2.6 - 12.77), and it remains significant also after other variables such as previous head injuries, pesticide exposure and smoking are controlled. Our results (*Study 1*) confirm the presence of familial aggregation in significantly higher percentages of consecutive PD cases compared to controls. These together suggest that familial aggregations are not incidental but more likely reflect a shared, genetic, environmental or mixed etiology.

The discovery of MPTP-induced parkinsonism renewed interest in the environmental hypothesis of PD, but other exogenous toxins have not yet been identified.[27] Moreover, the absence of geographical clusters and secular changes in the incidence of PD suggest that if exogenous toxins exist, exposure in time and space is evenly spread.[27] The absence of intrafamilial correlation for year of PD onset, together with the presence of good intrafamilial correlation for age of PD onset, found in this and a previous study,[15] point against a shared acute environmental insult as an etiological mechanism in familial PD. However, chronic exposure to a common toxin plus a genetically determined risk would be in accordance with the observed findings, once again highlighting the role of genetic factors.

In keeping with other studies,[10,15,16] we found a significantly higher frequency of positive family history for tremors among PD cases than in spouse controls. These data, together with recent PET evidence of disruption of nigrostriatal pathways in cases of isolated rest tremors,[28] suggest that the familial aggregation of PD

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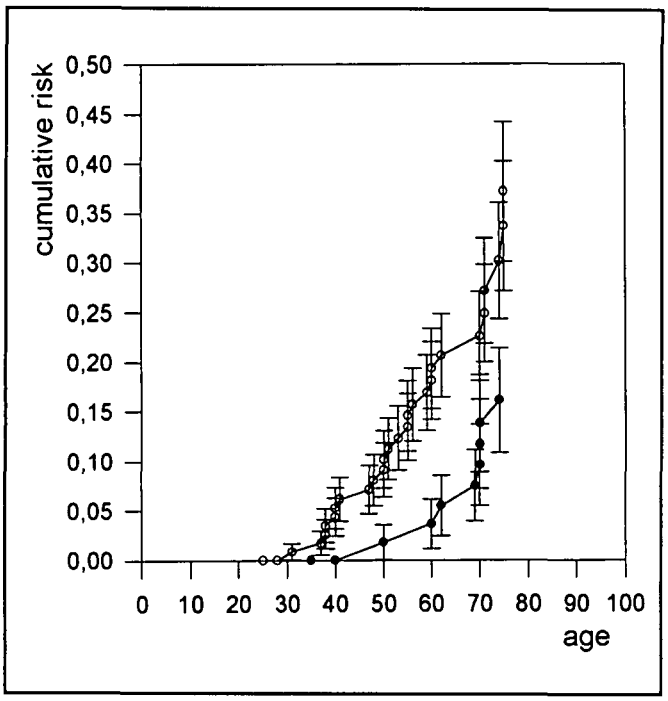

Figure 1: Estimated cumulative risk of PD (± standard errors) for non-proband siblings of multigeneration (●) and monogeneration (○) families.

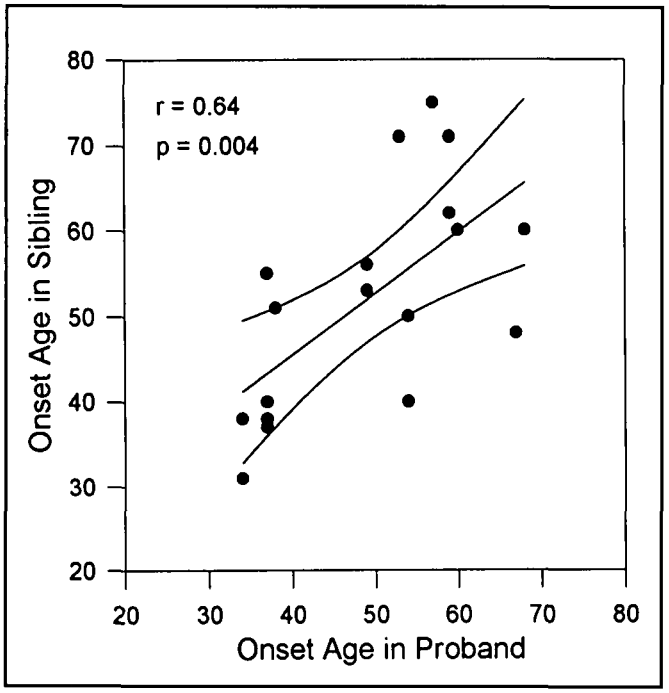

Figure 2. Estimated cumulative risk of PD (± standard errors) for siblings (○) and for parents (●) of probands within the 22 multicase families.

and tremors may reflect a common etiology, as suggested by Mjones.[12] Moreover, the problem of the clinico-pathological range of PD is further complicated by the demonstration of pathologically typical cases showing atypical clinical features, including cases of Lewy Body isolated dementia.[29-31] On the other hand, we recognize that the clinical diagnosis of Lewy Body disease is not always accurate.[32]

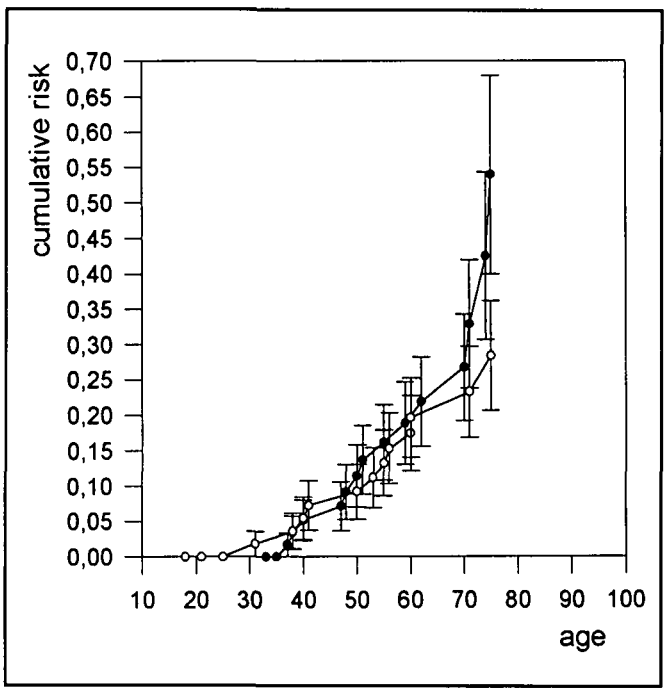

Figure 3: Linear regression analysis of the age of PD onset in probands and each of their affected siblings.

Comparison between familial and sporadic PD

The relationships between familial and sporadic PD cases remain obscure. The familial PD cases from our consecutive series (*Study 2*) showed an earlier onset when compared with sporadic ones, but Maraganore et al.[15] found no clinical differences between their familial cases and the sporadic cases from another published series. In some sporadic cases family links might be overlooked because of scarcity of familial information, reduced size of sibships in modern families, and especially if the antecedent carriers had died before symptoms had appeared. Our finding of earlier onset in familial cases would be in keeping with this last point.

The recent work by Lazzarini et al.[16] showed that the percentage of familial cases correlates with the completeness of family history. On the other hand, some familial aggregations might be examples of coincidental multiple sporadic cases.[11] The true magnitude of familial occurrence in PD has never been measured in population-based studies, and the hospital-based data may be biased toward familial cases.

Previous clinical genetic studies on PD

There are only a few systematic clinical genetic studies on PD. The first one, from Sweden on 194 PD cases and their families, concluded that PD is transmitted as an autosomal dominant disease with 60% penetrance.[12] This study was criticized for the including isolated tremors and clinically atypical cases.

Martin et al.[13] studied 130 PD probands and found significantly higher frequencies of PD among both parents and siblings of probands than in spouse controls. They also noted that siblings of probands with an affected parent had a lifetime

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cumulative PD risk of 29.7% by age 74, a significantly higher figure than that for the cumulative risk for siblings of probands without an affected parent (3.3%) or siblings of controls (4.3%). Considering all their PD cases as a whole (familial and sporadic), these authors suggested a polygenic model of inheritance.

Kondo et al.[14] re-examined the data of Mjones along with those of 263 PD cases from Minnesota. They measured PD frequencies of 9.7% and 11.7% among siblings of US and Swedish probands, as compared to expected figures of 0.9% and 0.7%, which they obtained by using prevalence rates for PD in Minnesota. They concluded with a multifactorial model of inheritance as the most likely explanation, with a heritability coefficient of 0.79, according to Falconer's method.

More recently, Maraganore et al.[15] studied 20 non-random families with at least two living affected PD cases. They calculated crude segregation ratios of 0.171 ± 0.043 and 0.286 ± 0.072 in siblings and parents of multicase family probands. Ancestral relatives were all unilaterally distributed. A good correlation emerged between onset age but not between year-of-onset in couples of PD relatives. They suggested an autosomal dominant inheritance of one or more genes with reduced penetrance as the most likely explanation.

Lazzarini et al.[16] studied 211 consecutive PD cases and noted a significantly higher risk for siblings of cases with an affected parent, similar to that reported by Martin et al.[13] Moreover, among 80 non-random multicase PD families, they measured similar crude segregation ratios among siblings and parents (0.21 ± 0.029 and 0.24 ± 0.033 respectively) and, more importantly, similar lifetime cumulative risks approaching 0.5 (0.42 ± 0.064 for siblings and 0.45 ± 0.07 for parents). These observations strongly support autosomal dominant inheritance with age-related penetrance. Ancestral relatives were again unilaterally distributed. Payami et al.[33] found a significantly higher lifetime cumulative incidence of PD among first-degree relatives of 114 PD patients than in first-degree relatives of controls.

Comparison between mono- and multi-generation PD families

The higher proportion (10/22) of monogeneration families in our *Study 3,* compared to previous reports (5/20 in Maraganore et al.;[15] 11/80 in Lazzarini et al.),[16] probably reflects the lack of information on second degree relatives in our monogeneration families. In fact, in all but 3 of these cases the proband and their relatives were unable to give complete information on the health status of their second degree relatives; in some cases the relatives had emigrated or had lost contact, in others the probands had no memory of their grandparents, aunts or uncles. These difficulties are shared by similar studies performed in diseases characterized by a late onset.[2,34]

Our criteria for inclusion of families were more restrictive than those used in the study of Lazzarini et al.,[16] who also included families with secondary cases only on the basis of "review of medical records or reliable family report". We included only families with at least two living and personally examined cases, and excluded those with only affected relatives by history. This reduced the number of multigeneration families that could be included.

Because the clinical features are similar, and the lifetime cumulative curves in siblings of probands of monogeneration and multigeneration families are superimposed, these two groups are likely affected by the same disease.

Pedigree and segregation analyses

Within our 22 families, the sex distribution of PD cases and ratios of paternal versus maternal transmission are similar. Taken together with previous studies,[15,16,35,36] this points against a sex-linked or mitochondrial inheritance.

The fact that the crude segregation ratios are low and not statistically different for parents and siblings confirms the results of previous studies and is consistent with both an autosomal dominant inheritance with reduced penetrance and a multigenic-multifactorial model.[13-16] The lifetime cumulative incidence of PD showed an increasing risk with age for both parents and siblings. The last case occurred at age 75 among siblings and 74 among parents, enabling us to estimate a cumulative risk approaching 0.4 for siblings and 0.2 for parents. The curve of cumulative risk for parents is moved to the right by about 15 years (Figure 2), and if data were available for oldest ages it might well approach values of 0.4-0.5. These findings suggest an autosomal dominant inheritance whose true penetrance is obscured by the late onset of the disease and by the competing effect of other causes of mortality, particularly in the parental generation. In the only previous study with similar analyses,[16] the lifetime risks for parents and siblings were found to be very similar and close to 0.4-0.5. Many more families are needed both to confirm the trend of an earlier onset in sibling generations using lifetime cumulative risks, and to analyse the same-sex transmission preponderance observed by others,[16] by generating cumulative curves among sons and daughters of affected mothers and fathers separately.

In our study, crude segregation ratios and cumulative lifetime risks in siblings of monogeneration families would also be in keeping with autosomal recessive inheritance, which predicts a risk of 0.25 for siblings without affected parents. However, clinical features, crude segregation ratios and cumulative lifetime risks in monogeneration and multigeneration families are similar. We observed only two instances of consanguinity: one in parents of one monogeneration sibship and the other in a family with clear vertical transmission in 3 generations. These considerations, together with the scarcity of information on second degree relatives of these patients suggest that autosomal recessive inheritance is unlikely, even if it cannot be ruled out.

Monogenic / multigenic models

Based on the analysis of ancestral relatives, Young et al.[37] suggested multigenic inheritance in the series of Mjones[12] and Martin et al.[13] Their conclusion has been later questioned and data reinterpreted to support a monogenic inheritance.[38] Ancestral cases of PD relatives and their pairs, according to the method of Slater et al.,[25] are all unilaterally distributed, in this and in the previous reports[15,16] suggesting a monogenic dominant model.

Onset age considerations

Haldane[39] postulated that for diseases caused by only one major gene, the intrafamilial correlation of onset ages is expected to be very high, with coefficients approaching unity. If different genes were responsible in different families, the onset age would show a better intra-familial than inter-familial correlation. Correlation coefficients around 0.5 would be expected for a disease whose onset age is controlled by one main gene plus other modifying genes. Finally, the coefficients would be even lower

in the cases of strong environmental influences on onset age. In our subjects, onset ages show a significant intra-familial correlation ($r = 0.475$, $p = 0.009$), an observation similar to that made by Maraganore et al.[15] The intra-sibship correlation for onset age in our series is even better ($r = 0.64$, $p = 0.004$). All these data are compatible with the presence of one main gene plus other genetic and/or non-genetic modifiers of onset age.

The intra-generational variance of onset age is significantly lower than the inter-generational one. This means that the onset age is similar in sibships of one family but is more variable within multiple generations. In 8 out of the 9 instances of parent/child couples of PD cases we observed, the onset was earlier in the offspring – "anticipation" phenomenon.[20]

It may be difficult to distinguish between true anticipation phenomena and case sampling biases. Because PD is generally a late-life disease, those who are young at the time of ascertainment, would be more likely to have living affected siblings, parents, and other relatives than the usual late onset probands. A tendency for PD families to be ascertained via a young-onset proband in the most recent generation could therefore be present, thus biasing the composition of the sample for the anticipation analysis. This effect cannot be excluded in our study. Moreover, among the families we ascertained, many members of the younger generations might not have lived through the entire age of risk, and fewer cases of late onset would thus be observed in the new generations. Another source of bias is the possibility that early-onset cases have a reduced reproductive capacity, and would, as a result, only be observed as members of the new generation. Although the control of all these potential biases is difficult, the Kaplan-Meier method provides some clues. When considering the cumulative risk curves shown in Figure 2, we can assume that the late-onset cases among siblings, and/or the young-onset cases among parents have been underestimated. The former seems unlikely, as the curve for siblings is already approaching its maximum theoretical value of 0.5, and more late-onset cases would increase the cumulative risk even further. The latter possibility seems more realistic, and more early-onset cases among parents would move the parent curve closer to that for siblings. However, PD onset is very rare before age 30. It can therefore be reasonably assumed that it does not reduce reproductive capacity.[27] In our series there were 2 cases with onset before age 30 and both had already had children. All these considerations suggest the presence of a true anticipation phenomenon in our families. The lifetime incidence curve showing a different age of risk for parents and siblings could be seen as a confirmation of this pattern. Anticipation of onset age has been suggested in two large kindreds with autosomal dominant, autopsy-proven PD.[8,40] Recently, the expansion of unstable DNA trinucleotide repeats (dynamic mutations) was found to cause various neurogenetic disorders displaying anticipation, including Huntington's disease, myotonic dystrophy, spinal and bulbar muscular atrophy, fragile X mental retardation (FRAXA and FRAXE), spinocerebellar ataxia (SCA1), dentatorubral-pallidoluysian atrophy (DRPLA) and Machado-Joseph disease.[41-48] The DNA expansion hypothesis must therefore be actively explored in familial PD cases.

Conclusions

Our study confirms that a positive family history for PD or for PD and tremor is significantly more common among PD patients than controls. Familial PD patients had an earlier onset when compared with sporadic ones from the same consecutive series. Our clinical genetic data are consistent with a monogenic autosomal dominant model of inheritance in familial PD, with a strongly age-related penetrance. Although a sampling bias cannot be excluded, anticipation of onset age is evident in some families.

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