

# Parkinson's Disease: A Genetic Study

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**ABSTRACT:** A sample of 122 patients with Parkinson's Disease was studied for the purpose of investigating if the frequency of relatives affected with Parkinson in this group was higher than in a control group and to see if the genetic load was more important in some of the subtypes of Parkinson described by Barbeau and Pourcher (1982).<sup>7</sup> In our 122 patients, we found that 1.7% were post-encephalic parkinsonian, 12.3% were symptomatic cases and 86% of the idiopathic variety. There were 16.1% early onset patients in the idiopathic group and among these we found 23.5% with a positive family history of Parkinson in the first-degree relatives. In 6 cases with the tremor onset form of the disease, the family history was positive and 5 patients, 4.7% had familial essential tremor-related Parkinsonism. Our results support Barbeau's hypothesis<sup>7,19</sup> that Parkinson is a heterogeneous disease in which some subtypes (such as early onset Parkinson) have an important genetic susceptibility component.

**RÉSUMÉ: Maladie de Parkinson: une étude génétique.** Un échantillon de 122 patients souffrant de la maladie de Parkinson a été étudié dans le but d'examiner si la fréquence de la maladie de Parkinson est plus élevée dans leur parenté que dans un groupe témoin et pour voir si le fardeau génétique est plus important chez certains des sous-types de Parkinson décrits par Barbeau et Pourcher (1982).<sup>7</sup> Parmi nos 122 patients, 1.7% présentaient un Parkinson post-encéphalitique, 12.3% présentaient un Parkinson secondaire et 86% un Parkinson idiopathique. Chez 16.1% du groupe idiopathique, le début de la maladie était précoce et parmi ceux-ci, 23.5% avaient une histoire familiale positive de maladie de Parkinson chez des membres de leur famille apparentés au premier degré. L'histoire familiale était positive chez 6 cas présentant la forme à début tremblant, alors que 5 patients, soit 4.7% des cas avaient une maladie de Parkinson reliée à un tremblement essentiel familial. Nos résultats supportent l'hypothèse de Barbeau<sup>7,19</sup> que le Parkinson est une maladie hétérogène dont certains sous-types (tel que la maladie de Parkinson à début précoce) ont une composante de susceptibilité génétique importante.

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Ever since Parkinson described Paralysis Agitans in 1817, the question of the possible genetic origin of the disease has been raised. Different models of heredity have been proposed: an irregular dominant mode of mendelian transmission<sup>1</sup> an autosomal recessive mode in some pedigrees<sup>2</sup> and a multifactorial model by most authors.<sup>3,4,5</sup> Others, like Duvoisin (1984),<sup>6</sup> conclude that no genetic component is involved and that the results are due to chance occurrence only.

That Parkinsonism may be a syndrome rather than a disease entity has been considered for many years and some authors divide the patients with Parkinsonism into three groups: post-encephalitic, symptomatic and idiopathic Parkinsonism. Most genetic studies have involved the idiopathic group, which may not be homogeneous.

Martin (1973)<sup>4</sup> pointed out that when the available genetic data for Parkinson's disease fits an acceptable model, this does not provide proof that all cases of the disease are genetically determined or that the clinical syndrome of the idiopathic form reflects a specific homogeneous clinical or biochemical entity.

Recently Barbeau et al (1982)<sup>7</sup> emphasized that idiopathic Parkinson's disease is not homogeneous and that within the large idiopathic group there exists one or more sub-groups,

such as early onset Parkinsonism patients who have an important genetic load, while others are without major genetic components.

This report describes the results of a familial aggregation study in a group of Mexican patients with Parkinson's disease and the sub-groups that we found in agreement with Barbeau's classification (1982).

## METHODS

The index cases were 122 patients with Parkinson's disease obtained from the outpatient clinic of the National Institute of Neurology and Neurosurgery (I.N.N.N.) of Mexico City. All patients were examined by a neurologist. The diagnosis of Parkinson's disease was based on the presence of a constellation of signs which included at least two or more of the following: tremor, rigidity, bradykinesia and impaired postural stability. None were selected because of known family history of Parkinson's disease. The control groups consisted of the spouses of the index cases and some individuals that work in the Institution.

After the standard consultation, all patients and controls were interviewed by one of us to perform a careful pedigree

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focussed only on first degree relatives since it was not possible to obtain accurate information of more distant relatives. Criteria for the diagnosis of Parkinson's disease in a family member who was not available for examination included at least one of the following; diagnosis by a physician, an adequate description by a relative which included at least tremor and abnormal gait or rigidity. If there was doubt about the diagnosis the individual was assumed to be unaffected.

**RESULTS**

The sample consisted of 122 Mexican adult patients, 52 female and 70 male probands. The control group contained 50 men and 50 women matched for age and sex.

The mean ages of the female and male probands at the onset of the disease were 51.8 and 51.4 years respectively; if the early onset group were excluded, the mean age onset was 55.6 years and the mean age at onset in the early onset group was 29.7 years.

For the familial aggregation calculation we excluded 15 patients with symptomatic Parkinsonism (12.3%) and 2 others with post encephalitic Parkinsonism (1.7%); interestingly, none of these 17 patients had familial aggregation. The rest of the 105 patients (86%) were considered idiopathic. In agreement with the classification proposed by Barbeau in 1982,<sup>7</sup> our 122 patients were sub-grouped as seen in Table 1.

In the idiopathic group we found positive familial aggregation in first degree relatives in 9.5% of the probands and 1% in the controls. Of the 105 index cases, 17 (16.1%) had juvenile parkinsonism (term used by Yokochi and Narabayashi)<sup>9</sup> or early onset Parkinsonism (onset before their 40th birthday). In this sub-group, four patients with typical features of Parkinson

disease (23.5%) had familial history of Parkinson in first degree relatives (Figure 1, Table 2), and two more patients in this group had one second degree relative with Parkinson disease undergoing treatment in our Institute.

We found 6 index cases, with onset after 40 years, with Parkinson that began with tremor and persisted with it as the most important feature of the diseases who showed a positive family history of Parkinson in first degree relatives. (Table 3). In cases 1, 2, 4, 6, 7 and 10, the first degree relative affected was examined by one of us and all had typical features of Parkinson disease, in cases 1 and 2, the two affected sisters also had onset of the disease before age 40.

In four cases, (3, 5, 8 and 9), in which the affected relatives were dead and there were no CAT scans, nor autopsy confirmation, the diagnosis was based solely on the description by the relatives. All of these affected relatives had onset of this disease after 40 years.

While 5 other patients (4.7%) had family history of essential tremor with apparent dominant inheritance of the essential tremor within their families, in four cases at least one first degree relative in each family was examined by one of us and the diagnosis of essential tremor confirmed (Figure 2). In the control group, there were no cases of essential tremor. Consanguinity was 3.8% in our experimental sample and 2.9% in the control group.

In the symptomatic group, the final diagnosis can be seen in Table 4.

**DISCUSSION**

The onset age in males and females proband is similar to that reported by other authors.<sup>8,10</sup> Eighty six percent of the index

**Table 1: Classification of 122 patients with Parkinson's Disease based on the Classification by Barbeau et al (1982)**

Type	Type	No. of Patients
Type I	Post-Encephalitic	2
Type II	Idiopathic	
	IIa Tremor onset Form	57
	IIb Akineto-Rigid Onset Form	20
Type III	Genetic	
	IIIa Familial Metabolic Akineto-Rigid Syndrome	0
	IIIa' Familial Tremor Onset Form	6
	IIIb Familial Essential Tremor related Parkinsonism	5
	IIIc Familial Juvenile Parkinsonism	17
Type IV	Symptomatic	15

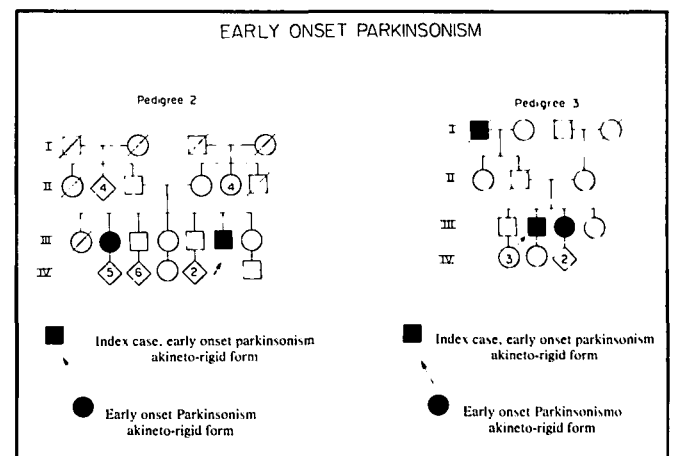


Figure 1 — Pedigree of two kinship with familial early onset Parkinsonism.

**Table 2: Familial Early Onset Parkinsonism**

Case	Type	Age of onset	Duration	First degree affected relative	Relative age of onset	Type
1	Akineto-rigid form	14	16	Sister	26	Akineto-rigid Form
2	Akineto-rigid form	24	4	Sister	31	Akineto-rigid Form
3	Akineto-rigid form	39	2	Mother	60	?
4	Akineto-rigid form	38	8	Father	65	Akineto-rigid Form

**Table 3: Familial Parkinsonism**

Case	Type	Age of onset	Duration	First degree affected relative	Relative age of onset	Type
5	Tremor form	47	16	Mother	50	?
6	Tremor form	47	5	Father Sister	? 50	Tremor-Form
7	Tremor form	67	7	Sister	68	Tremor-Form
8	Tremor form	49	7	Brother	58	?
9	Tremor form	45	10	Brother Sister	60 55	?
10	Tremor form	57	5	Sister	65	Tremor-Form

**Table 4: Diagnosis in 15 patients with symptomatic Parkinson**

Diagnosis	No. Patients
Parkinson induced by drugs	1
Shy-Drager Syndrome	1
Parkinson-Dementia Syndrome	1
Basal ganglia calcification	1
Arteritis	1
Cysticercosis	4
Lues	3
Multiple cerebral infarctions	3

cases were of the idiopathic variety, similar to that reported in other series,<sup>11</sup> i.e. 85.7%.

The familial incidence in first degree relatives of Parkinson patients was 9.5% in this group of 105 patients with idiopathic Parkinson; this is similar to the reports of other authors, Barbeau (1982)<sup>7</sup> for example, in 300 patients with Parkinson, reported a 13% positive family history in first degree relatives.

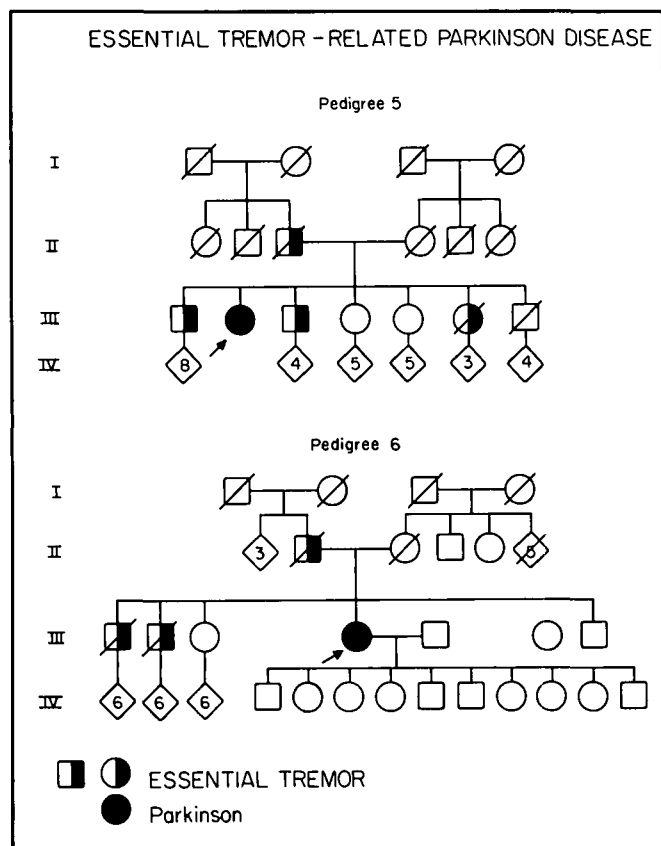
We found early onset Parkinsonism in 16.1% of our sample, Yokochi and Narabayashi (1981)<sup>9</sup> reported a frequency of such cases in Japan between 10 and 18% of all Parkinsonians and Barbeau et al (1982)<sup>7</sup> 9.4%, these figures are similar to our own findings.

In this series, the early onset sub-group had an important genetic-predisposition; in these patients the incidence of positive family history was 23.5% which we consider is a significantly elevated incidence, although it is not as high as that found by the Japanese authors<sup>9</sup> (42.5%) and by Barbeau et al (46%).<sup>7</sup>

We also observed a sub-group of patients with onset of the disease with 40 years of age and predominance of tremor (sub-group IIIa' Table 1), with an important familial incidence. Zetusky et al (1985),<sup>10</sup> found that the tremor sub-group was often associated with a family history of Parkinsonism, confirming the findings of Roy et al (1983).<sup>12</sup> Five of our families were found to have cases of both Parkinson and essential tremor. We do not have studies about the prevalence of essential tremor in the Mexican population, but in our control group there were no cases of essential tremor.

A slightly higher consanguinity rate is observed in the Parkinson group than in the controls, as reported by Roy et al 1983.<sup>12</sup> We found consanguinity in three early onset non-familial patients, one familial early onset and one with the non-familial tremor form.

The problem of the heritability of Parkinson's disease has been discussed for many years and it is still subject to controversy. Some authors like Barbeau (1982, 1984)<sup>7,18,19</sup> are in favour of component of genetic susceptibility and others like Duvoisin et al (1981, 1984),<sup>6,13</sup> negate any genetic component to the disease. The existence of some hereditary disease like autosomal dominant olivopontocerebellar atrophy type V, hereditary mental depression and taurine deficiency in which Parkinsonism is part of the clinical picture of the disease, is an indirect evidence of the presence of different genes that, in some way mimics Parkinsonism.<sup>14</sup>



**Figure 2 — Pedigree of two families with Parkinson's disease in association with hereditary essential tremor over 2 generations.**

Our results support the hypothesis that Parkinson is a heterogeneous disease and that the genetic component is different depending on the sub-group. Nevertheless our sample is too small to carry out proper genetic analysis. In the symptomatic group of patients, it is of interest to point out that in Parkinsonism induced by drugs, Myriantopoulos et al (1969)<sup>15</sup> found a 2.5% frequency of affected relatives in 486 Parkinson disease index cases versus only 0.6% in 483 relatives of control subjects. In this study, we had only one patient with Parkinson induced by drugs and she did not have family antecedents of Parkinson.

In the symptomatic group (Table 4), we included some etiologic entities with a frequency not reported up to this time in other series. This probably depends on a regional frequency of specific pathologies. The most frequent etiology in this group was cysticercosis which corresponded to 3.2% of the symptomatic cases.

This variety must be included in the differential diagnosis of symptomatic Parkinson Syndrome in our country where cysticercosis is an important cause of nervous system affection.<sup>16</sup>

The heterogeneity of Parkinson disease and its multiple causes is manifested again in the report of Langston and Ballard (1983),<sup>17</sup> where they describe the production of irreversible Parkinson in humans after the MPTP injection. As Barbeau (1984)<sup>18</sup> pointed out, it is possible that many people are constantly being exposed to products with a similar chemical conformation found in nature or industry.

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