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Is Parkinson's disease of early onset a separate disease entity?

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Summary. Two groups of patients suffering from Parkinson's disease were studied. The first group consisted of 23 patients with an onset age before 40 years; in the second group of 21 patients the onset was after age 50. The clinical findings and the course of the disease were very similar in each group. In spite of a longer disease duration in the patients with early onset of the disease there was no difference in motor impairment; the younger patients did better in mental testing and they were taking less dopaminergic medication. These differences are thought to be due to the age difference rather than to the existence of different disease entities. In the early onset group more familial cases (mostly affecting siblings) were found than in the older ones. The points in favour of there being a hereditary subgroup of early onset Parkinson's disease or of environmental factors causing the disease are reviewed.

Key words: Parkinson's disease, early onset – Heredity – Environmental factors

Introduction

Juvenile or early onset Parkinson's disease (PD) is defined as having its onset before the age of 40 years [23]. It is still a matter of controversy whether it is to be considered merely as idiopathic PD with early onset or whether it is a disease entity of its own. The present study was conducted to find evidence in favour of one or the other of these alternatives.

Several earlier studies came to opposite conclusions. Yokochi et al. [25] considered it to be the same as late onset idiopathic PD. Gershanik and Leist [5], Lima et al. [10] and Quinn et al. [13] share this conclusion. On the other hand, Barbeau and Poucher [1], Barbeau and Roy [2] and Roy et al. [18] have divided PD into several subgroups. At least three of these groups with an early onset are said to be hereditary. Besides familial juvenile parkinsonism they defined an akinetorigid syndrome combined with familial metabolic disturbances, and the cases with tremor onset as having a high incidence of essential tremor in their families.

Patients and methods

Two groups of PD patients with different ages of disease onset have been included in the present study. Twenty-three patients (11 men, 12 women) were in group I, with onset before the age of 40 years. In the 21 patients (11 men, 10 women) of group II the first symptoms of idiopathic PD arose after the age of 50. We have chosen a minimal onset age of 50 rather than 40 years for this group for the following reason: although early onset PD is defined as beginning before the age of 40 years [23], there is no compelling biological reason for this age limit. We wanted to exclude as far as possible a masking of potential differences between the two groups by patients being attributed to the wrong group by virtue of the above definition.

All the patients underwent the same examination: a complete history, a clinical examination and a mini-mental test. The patients were particularly questioned about their family history, the onset and the course of the disease, as well as earlier illnesses and contacts with toxic or potentially toxic agents. We tried to collect as much information as possible concerning the treatment during the course of the disease and on the side-effects, especially on involuntary movements and on-off phenomena. The actual impairment by PD was determined with the help of Webster's score [22], the Hoehn and Yahr stages [7] and the activity-in-daily-life (ADL) score according to Schwab and England [20]. For the neuropsychological assessment a modified mini-mental test [4] was used. The original test was slightly extended as, in particular, was the timing of the tasks eliminated. The maximum score was 50 points.

For statistical analysis Student's t-test for independent samples and, where appropriate, the chi^2 test have been used.

Results

Onset and course of PD

The mean age of group I patients at onset of PD was 33.5 years (SD 6.7 years); its mean duration was 14.9 years (SD 6.6 years). The respective values for group II patients were 57.8 years (SD 6.1 years) and 10.9 years (SD 6.7 years). The difference of disease duration between the two groups was at the limit of significance ($P = 0.053$). The most important data concerning history and clinical findings are summarized in Tables 1 and 2. The initial symptoms were the same in both groups; in particular, the number of patients experiencing dystonias before receiving antiparkinsonian treatment was identical in both groups.

In group I, 7 patients had noticed tremor as the first symptom, 7 had an ill-defined sensation of weakness, 6 had impaired motility or stiffness and 4 a gait disturbance. In the older patients (group II) tremor was first noticed in 9 cases; 5 patients had gait disturbances, 4 a sensation of weakness; 4

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Table 1. Patients' data, motor impairment and mini-mental test in patients with early (group I) and with later (group II) onset of Parkinson's disease (PD)

	Group I ($n = 23$)		Group II ($n = 21$)		P
	Mean	SD	Mean	SD	
Age	48.5	6.1	68.7	5.1	< 0.01
Age at onset	33.5	6.7	57.8	6.1	< 0.01
Duration (years)	14.9	6.6	10.9	6.7	$= 0.053$
Webster score	12.4	5.0	13.8	6.4	NS
Hoehn-Yahr stage	2.7	0.6	3.1	1.1	NS
ADL score	77.4	9.0	69.5	17.9	NS
Mini-mental test	38.0	3.3	33.5	6.6	< 0.01

Table 2. Synopsis of the symptomatology, and the family as well as the case histories in patients with early (group I) and with later (group II) onset of PD

	Group I ($n = 23$)	Group II ($n = 21$)	P
Tremor at onset	13	13	NS
Onset unilateral	23	18	NS
Dystonias at onset	3	3	NS
Fluctuations	22	18	NS
– On-off phenomena	5	9	NS
– Freezings	13	13	NS
– Wearing-off phenomena	16	9	NS
Pain	10	9	NS
Depression	6	6	NS
Frequent falling	12	11	NS
Memory loss	7	12	NS
Learning deficit	12	10	NS
Stereotaxic operation	7	0	< 0.01
Family history, positive for			
– Parkinson's disease			
First-degree relatives	5	1	NS
Siblings	4	0	< 0.01
– Hypertension	15	5	< 0.01
– Diabetes	9	3	NS
– Thyroid diseases	2	2	NS
First year of life in			
– Rural area	17	13	NS
– Urban area	6	8	NS
	$P < 0.01$	NS	

other patients suffered first from painful shoulder stiffness and 1 observed a progressive micrographia.

Patients of group I had more frequently spent their first years of life in a rural area rather than an urban one ($P < 0.01$). Also in group II more patients grew up in the country rather than in a town; this difference, however, was not significant. In neither of the groups had any patient had encephalitis or suffered from a severe head injury. In group I, 4 patients and in group II 3 patients had been exposed to pesticides, herbicides or organic solvents for a considerable period of time. None of these patients had ever suffered from apparent intoxication. In group I, 13 patients had never smoked and another 7 had not smoked for at least 5 years. The respective numbers for group II were 14 and 7.

Of the 12 younger female patients, 5 had experienced a worsening of parkinsonian symptomatology shortly before and during menstruation. Only 2 patients became pregnant after the onset of the disease. One of these patients noticed a transient worsening during pregnancy; otherwise, both pregnancies and deliveries were uneventful.

Family history

Out of 23 of the younger patients, 5 had first-degree relatives suffering from PD. In 4 of these cases one or more siblings had the same disease, confirmed by us or another experienced neurologist (Table 3). With the exception of patient 4's family no other cases of PD could be found among the relatives at risk of these patients. Patient 4 had consanguineous paternal grandparents; 3 of her first cousins suffer from PD. The 4 patients and their 8 diseased brothers and sisters have a total of 26 children, aged from 12 to 30 years. None of these children is known to have PD. Of group II only 1 patient reported that her mother had suffered from the same condition; in none of these cases have siblings been afflicted. Significantly more of the patients in group I have relatives suffering from arterial hypertension than in group II ($P < 0.01$); no such difference was found for diabetes or for thyroid disease. One patient in group I and none in group II had relatives with essential tremor.

None of the 5 familial cases in group I had dystonic or dyskinetic movements prior to the onset of L-dopa treatment and the illness did not start in childhood. They can thus not be considered as belonging to the syndromes described by Segawa et al. [21] and by Nygaard and Duvoisin [12].

Table 3. Family data of four early onset PD patients who have at least one affected sibling. Definite PD = diagnosis established by us or an experienced neurologist; probable PD = diagnosis by a general practitioner; healthy siblings have not been examined

Patient no.	Age at onset (years)	Siblings with		Healthy siblings	Other relatives with PD	Remarks
		definite PD (age at onset in brackets)	probable PD (age at onset in brackets)			
1.	29	3 (37, 40, 52)	–	3	–	Rural area Well water
2.	35	1 (40)	1 (40)	8	–	Rural area Well water
3.	29	1 (51)	–	4	–	Rural area Well water
4.	34	1 (47)	1 (41)	3	3 first cousins	Consanguinity of paternal grandparents Rural area Well water

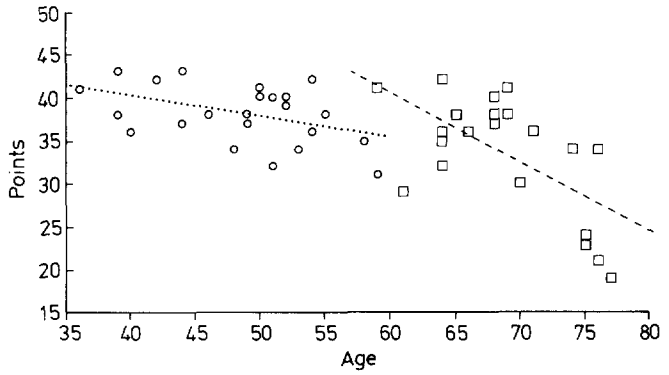

Fig. 1. Correlation between mini-mental test and age. Group I (○): $r = -0.47$, $P = 0.027$, regression I (·····); group II (□) $r = -0.63$, $P = 0.003$, regression II (---)

Motor impairment

There was no significant difference with regard to impairment, which was assessed according to three rating scales between the two groups (Table 1). However, all three mean values were slightly better for the younger patients in spite of the longer duration of their disease. In group I neither of the three rating scales correlated significantly with disease duration (Webster: $r = 0.26$, $P = 0.24$; Hoehn-Yahr: $r = 0.25$, $P = 0.24$; ADL: $r = -0.40$, $P = 0.06$). In group II disease duration and the Hoehn and Yahr score ($r = 0.63$, $P = 0.002$) as well as the ADL scale ($r = -0.68$, $P = 0.001$) were significantly correlated. The respective values for the Webster scale were: $r = 0.36$, $P = 0.10$.

Neuropsychological tests

In the mini-mental test the older patients did significantly worse than the younger ones ($P = 0.0082$) (Table 1). The individual values correlated significantly with age in both groups, the regression being steeper in the older patient group than in the younger one ($P < 0.05$) (Fig. 1). In group I there was no significant correlation of the mini-mental test either with disease duration ($r = -0.14$, $P = 0.51$) or with its severity (Webster: $r = -0.25$, $P = 0.27$; Hoehn-Yahr: $r = -0.12$, $P = 0.60$; ADL: $r = 0.12$, $P = 0.60$). On the other hand, in group II the mini-mental test correlated significantly with the Webster score ($r = -0.58$, $P = 0.005$) as well as with the ADL scale ($r = 0.46$, $P < 0.05$). The correlations between mini-mental test and the Hoehn and Yahr staging ($r = -0.412$, $P = 0.06$) and the disease duration respectively ($r = -0.39$, $P = 0.07$) did not reach the level of significance.

Treatment and side-effects

The data concerning the treatment and its side-effects are summarized in Table 4. In order to obtain a measure for the total dopaminergic therapy, we added 100 mg for each 10 mg bromocriptine to the daily dose of L-dopa plus decarboxylase inhibitor according to Riopelle et al. [17]. In group I, treatment duration was significantly longer than in group II ($P < 0.05$), whereas the daily doses of antiparkinsonian compounds were very similar in both groups. The treatment was initiated after a mean disease duration of 1.5 years in both groups. None of the older patients had undergone stereotaxic thalamotomy, while this had been performed in 7 out 23 patients in the younger group ($P < 0.01$). Side-effects such as dyskinesias, dystonias and hallucinations occurred with the same frequency in both groups. In group I dyskinesias had appeared at a significantly lower daily dose of dopaminergic therapy ($P = 0.025$).

Discussion

The onset of the disease was very similar in our patients with early (before age 40 years) and later onset of PD; tremor, gait disturbances, a sensation of weakness and impaired movement were mentioned as initial symptoms. This observation is in agreement with that of Yokochi [23], when taking into account that the dystonias which he saw frequently in his patients occurred mainly in those with an onset age below 14 years. We have not seen patients with such an early onset, the earliest one beginning at 16 years. All patients in group I and 18 out of 21 in group II had unilateral onset of symptoms.

In spite of the longer duration of PD in group I, its severity was very similar in each group. This speaks in favour of a slower progression and a less severe impairment of patients with early onset, as already described by Yokochi et al. [25]. This conclusion is supported by the observation that the daily

Table 4. Treatment and side-effects of treatment in patients with early (group I) and with later (group II) onset of PD

	Group I			Group II			*P*
	n	Mean	SD	*n*	Mean	SD	
Duration of treatment (years)	23	13.6	6.7	21	9.4	6.8	<0.05
L-Dopa (mg/day)	42	583.1	298.7	21	632.5	270.2	NS
Bromocriptine (mg/day)	11	18.4	15.2	12	12.8	7.4	NS
Dopaminergic treatment (mg/day)[a]	23	671.0	335.0	21	709.0	328.9	NS
Anticholinergics (mg/day)	14	10.6	10.8	6	6.8	4.8	NS
Dyskinesias, onset							
– after years of treatment	16	9.2	5.4	11	6.2	3.9	NS
– at dopaminergic dose (mg/day)[a]	16	677.2	360.6	11	1040.4	385.9	<0.05
On-off phenomena, onset							
– after years of treatment	10	10.3	5.7	9	7.3	3.8	NS
– at dopaminergic dose (mg/day)[a]	10	734.3	342.3	9	1062.5	390.3	NS

[a] For each 10 mg bromocriptine, 100 mg was added to the daily dose of L-dopa plus decarboxylase inhibitor [17]

doses of dopaminergic compounds are the same in both groups, although group I had significantly longer treatment periods. It seems that, because of the slower progression, the dosage of the dopaminergic compounds can be kept at lower levels than in group II patients. As reported by other authors [5, 13, 25], our early onset patients experienced drug-induced dyskinesias at a significantly lower dose level than the older ones. This might be an additional reason for keeping the dosage of dopaminergic compounds low.

The mean mental status was significantly worse in the patients with later onset than in group I. With more thorough psychological testing, Hietanen and Teräväinen [6] came to the same conclusion. In both groups the mental status was negatively correlated with age (Fig. 1), thus confirming earlier findings [6, 11]. The steeper decline in mental performance in the late onset group may be explained by the inclusion therein of four moderately to severely demented patients aged between 75 and 77 years. If these patients are excluded the regressions in the two groups become very similar.

Lieberman et al. [9] distinguished two separate disorders: one occurring in a younger population with an exclusively motor impairment, a more benign course and better response to L-dopa; and another where motor impairment is followed by a cognitive disorder occurring in an older population with a more rapid course and poorer response to treatment. Our findings discussed above are in perfect agreement with this definition. Nevertheless, we doubt whether such a subdivision is really justified. There are no fundmental, but rather gradual differences between the two groups and most, if not all of them could equally well be explained by the more advanced age of group II patients. In the sense of Kondo's [8] multifactorial hypothesis, motor and intellectual impairment as well as the rate of progression could be increased by the addition of "physiological" age-induced changes.

The four families in group I with a familial accumulation of PD deserve particular consideration. At first sight it is very tempting to assume a genetic aetiology in all these cases. In the family of patient 4 with consanguineous grandparents and with three affected first cousins, this assumption is very probably correct. It is astonishing, however, that in the other three families only siblings and no other relatives at risk suffering from PD could be detected. A toxic cause, even if no causative agent could be found, could very well explain these findings if it is assumed that a lesion has occurred in childhood. All these patients grew up on farms that had their own wells at that time. This coincides with the findings of Rajput et al. [15]: their patients with early onset PD in the province of Saskatchewan (Canada) were all raised in rural communities that had no central water supply. As far as we have been able to ascertain, very few pesticides or herbicides were used in Switzerland during the 1930s and 1940s.

An increased incidence of familial cases of PD with early onset has been found by several authors. Yokochi and Narabayashi [24] reported that 42.5% of their early onset patients had relatives suffering from PD. The figures given by Barbeau and Poucher [1], Gershanik and Leist [5], Lima et al. [10] and by Quinn et al. [13] are 37.5%, 23.1%, 9.5% and 25% respectively. The percentage in the present study is 21.7%. The overall incidence of familial case in these studies is 28.6% of 189 PD patients with early onset. The differences between the various studies may be due to the sample sizes, to methodological and possibly also to real geographic differences. Quinn et al. [13] found that their patients with onset before 21 years were invariably familial cases. Our two patients in this age group had no affected relatives at risk.

Yokochi and Narabyashi [24] stated that "familial incidence was mostly confined to siblings". In the series of Lima et al. [10] both familial cases were siblings. Also in the study of Quinn et al. [13], particularly in the patients with an onset age below 21 years, several siblings were affected. These authors found that "twenty percent of such patients (beginning between age 21 and 40 years) had at least one first- or second-degree relative in the same or antecedent generations with parkinsonism, but only 1.5% of their relatives at risk had parkinsonism". Based on this last figure, they felt unable to confirm an exceptionally high familial incidence of parkinsonism in the relatives at risk of the respective index cases. However, it should be taken into consideration that a relatively small subgroup with a genetic form of PD could be masked when looking at the entire population.

The striking accumulation of siblings (and to a lesser degree of parents) in familial cases in the present as well as in other studies evokes an alternative interpretation to the possibility of inheritance. As mentioned above, the possibility of a toxic cause active during childhood has to be taken into account. Our findings coincide with those of Rajput et al. [14–16] who postulated that childhood drinking water is a likely vehicle for such an agent. In six families with PD, Calne et al. [3] found the mean difference in the time of onset in different generations to be 4.6 years, while it was 25.2 years between children and parents. The authors concluded that this finding suggested an environmental rather than a genetic cause. Schoenberg [19] concluded that environmental aetiological factors probably play a role when he compared epidemiological data from the United States, from Nigeria and from the People's Republic of China.

We conclude that there are no fundamental differences between PD of early and of later onset. Most of the differences between the two groups can be explained by the additional age-induced changes in the older patient group. Thus early onset PD should not be considered as a disease entity of its own. The accumulation of familial cases in early onset PD suggests the existence of a genetically caused subgroup. There is, however, increasing evidence that environmental factors might be a causative factor in these cases.

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