Very Long-Standing Parkinson's Disease

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Dear Sir,

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the presence of motor and nonmotor symptoms [1]. Despite effective symptomatic treatment, most patients eventually deteriorate with the passage of time [1–13]. The progression of PD is not predictable for individual cases – the figures differ between studies, depending on the type of study and initial treatment. In general terms, roughly 50% of the patients will develop at least one motor or nonmotor complication within 5 years (including motor fluctuations, gait impairment, dyskinesias, loss of postural reflexes, altered behavior and dementia) [3, 5–8, 10]. These figures are even worse after the first decade; indeed, Hely et al. [11], who reviewed patients previously included in the Sydney Multicenter Study of Parkinson's disease, found that after 15 years of diagnosis, most patients were disabled and almost half exhibited criteria of dementia [11]. Based on this data, very long-standing PD patients – those with at least 20 years of PD progression – should be almost irredeemably disabled. To date, few studies have addressed this issue.

The aim of this study is to assess the motor and functional characteristics of very long-standing PD. We reviewed the medical records of patients with very long-standing PD, arbitrarily defined as those with disease duration of at least 20 years since diagnosis.

Patients and Methods

We reviewed the medical records at our institution going back to 1990 in search of all patients diagnosed at least 20 years prior as having PD. In all cases, the date of diagnosis was clearly established. PD was clinically defined according to the criteria of the Parkinson's Disease Brain Bank in the UK [14]. All these patients maintained an objective response to levodopa (LD) confirmed in every case. These patients were evaluated in an 'off' condition, before LD challenge, when possible. Evaluation was carried out by means of the Unified Parkinson's Disease Rating Scale, Hoehn-Yahr stage, and Schwab and England scale. Motor complications were assessed as follows: (1) drug-related dyskinesias, including 'on' and 'off' dyskinesias; (2) motor fluctuations defined as evident impairment of mobility bearing close relationship to the timing of medication, including wearing off; (3) gait abnormalities, including freezing of gait and festination, and (4) significant loss of postural reflexes interfering with function. For those patients treated with deep brain stimulation (DBS), evaluation was carried out in 'on' stimulation. Diagnosis of dementia was defined as cognitive deficits extensive enough to meet the DSM IV criteria [15]. Finally, the age at onset of these patients was compared with that of a group of typical PD patients who were prospec-

tively studied for 10 years (parametrical comparison, t test). The local ethics committee approved this work.

Results

We identified 24 patients (8 male, 16 female; mean age at diagnosis: 45.1 ± 10 years; present age: 70.8 ± 9.1 years; evolution in years: 25.6 ± 8) with very long-standing PD (>20 years of evolution). The age at onset of this group of patients (45.1 ± 10 years) was statistically different when compared with a group of 45 typical PD patients followed prospectively for 10 years (45.1 ± 10 vs. 58.5 ± 10.2 years; $p < 0.0001$, Student's t test), published recently [9].

Nine patients were treated with DBS (subthalamic stimulation in 7 of 9 patients, thalamic stimulation in 2 cases) because of motor fluctuations and/or severe rest and postural tremor, and 2 patients were treated with thalamotomy in the 1980s (cases 14 and 24). Epidemiological and clinical data are shown in table 1. Most patients had motor complications including motor fluctuations (22/24), freezing of gait (22/24) and loss of postural reflexes (21/24). Eighteen patients had dyskinesias (18/24), mainly mild 'on' chorea and 'off' dystonia; however, moderate or severe dyskinesias were present in 5 patients (cases 3, 12, 14, 17 and 21). Nine patients exhibited visual halluci-

Table 1. Clinical characteristics of very long-standing PD patients

Patient No.	Gender	Present age, years	Evolution, years	UPDRS (total)	UPDRS (motor)	MF	DYSK	FG	Dementia	DBS	Family history	HY stage
1	M	59	22	61	36	+	+	+	–	+	+	III
2	F	59	32	33	17	+	–	+	–	+	+	III
3	F	72	42	63	39	+	+	+	–	+	+	IV
4	F	71	22	66	44	+	+	+	–	+	–	IV
5	F	60	21	21	8	–	–	+	–	+	–	III
6	F	58	20	30	21	+	–	–	–	+	+	II
7	F	75	40	84	60	+	–	+	+	+	–	IV
8	F	76	49	77	49	+	+	+	–	–	–	IV
9	F	85	35	105	60	+	+	+	+	–	–	V
10	F	76	21	81	52	–	+	–	–	–	+	IV
11	F	66	24	71	45	+	+	+	–	+	–	III
12	M	64	20	77	44	+	+	+	–	–	–	III
13	M	70	20	92	60	+	+	+	–	–	+	IV
14	F	81	36	87	56	+	+	+	–	–	–	IV
15	M	85	25	89	60	+	–	+	+	–	–	IV
16	F	74	21	51	36	+	–	+	–	+	+	III
17	F	83	23	46	30	+	+	+	–	–	–	IV
18	F	81	23	118	62	+	+	+	+	–	–	IV
19	M	77	20	64	36	+	+	+	–	–	+	III
20	F	68	20	65	42	+	+	+	–	–	+	III
21	M	58	20	49	27	+	+	+	–	–	–	IV
22	M	79	20	60	30	+	+	+	–	–	–	III
23	M	60	25	89	60	+	+	+	+	–	–	IV
24	M	66	20	45	28	+	+	+	–	–	–	III

UPDRS = Unified Parkinson's Disease Rating Scale; MF = Motor fluctuations; DYSK = dyskinesias; FG = freezing of gait; HY stage = Hoehn-Yahr stage.

nations and/or altered behavior and 5 patients met the criteria of dementia. Nine patients had a family history of parkinsonism, including case No. 2, a carrier of the parkin gene mutation. In spite of these complications, one third of the patients (8/24) were independent in their basic daily activities or needed only minor help. Some of these patients had surprisingly good functional capacity (cases 2, 5, 6, 13 and 16).

Discussion

The majority of our patients with very long-standing PD had motor and nonmotor complications including motor fluctuation, freezing of gait, dyskinesias and altered behavior (e.g. hallucinosis or delirium). Despite these complications, one third of the patients (8/24) had reasonable functional status and some patients were

independent in their daily living activities (cases 2, 5, 6 and 16). Few studies have addressed the issue of very long-standing PD [2, 6, 7, 10, 11]. Yust-Katz et al. [10] identified 47 patients whose disease duration was more than 13 years; although 53% of the patients reached Hoehn-Yahr stage V in an 'off' condition, 14% had a relatively good functional status (<4 Hoehn-Yahr stage in an 'off' condition). Previous studies, including classic predopa articles, have suggested that about a third of patients are cases of mild disease [2]; these figures seem to have remained stable with the passage of time [3, 6, 13].

A substantial proportion (9/24) of our very long-standing PD patients underwent DBS due to motor fluctuations or severe tremor. Of these patients, 6 of 9 maintained a positive response to DBS at the time of the study. However, DBS does not essentially modify the long-term evolution of PD [15, 16] and probably cannot explain the rela-

tively benign evolution of our group of patients.

Interesting cases can be found in this group of very long-standing PD, such as patients maintained without LD, even after >20 years of evolution because of severe dyskinesias with very low-dose LD or patients with pure 'on' freezing. 'On' freezing is a well-known phenomenon, but it is very rarely seen in the absence of 'off' freezing [17, 18].

An important question is whether or not our group of patients with very long-standing PD is representative of the average PD population. Other studies on long-term PD (e.g. Hely et al. [11], Aarsland et al. [19]) have suggested a much faster progression, especially regarding the presence of dementia; however, the mean age at onset of these studies are clearly different, namely 56 years [11] and 64 years [19]. This contrasts with the earlier age at onset of 45 years observed in our series,

and this difference in age at onset is likely to explain, in part, this apparent controversy. It is of note that earlier-onset cases are overrepresented in this sample, and thus confirm previous findings from Selikhova et al. [20] and others [4]. According to Selikhova et al. [20], earlier-onset patients usually have relatively slow progression and the longest delay before the development of dementia, falling and need for residential care. Nevertheless, the average PD patient does not survive normally into the third decade of the disease [2, 11, 13, 20].

This work has several limitations. First, the sample size is modest. Second, most of

these patients with very long-standing PD patients were not prospectively studied from the start (some had a PD duration of >40 years), although we have followed some of these patients for over 20 years.

In summary, according to our data, very long-standing PD is not associated irremediably with very poor functional situation. Although most patients develop motor complications, dementia is not present in the majority of patients. This study confirms previous observations [20] which found that earlier-onset PD has a better average natural evolution than typical PD, which may explain the long evolution of this group of patients.

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