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Dyskinesias and motor fluctuations in Parkinson's disease

A community-based study

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Summary

We investigated the prevalence of dyskinesias and motor fluctuations, and the factors determining their occurrence, in a community-based population of patients with Parkinson's disease. Among 124 patients with Parkinson's disease, 87 (70%) had received a levodopa preparation. Among these 87 patients, 28% were experiencing treatment-induced dyskinesias and 40% response fluctuations. The prevalence of motor fluctuations was best predicted by disease duration and dose of levodopa, whereas dyskinesias could be best predicted by duration of treatment. Patients with a shorter time from symptom onset to initiation of levodopa and younger patients had developed motor complications earlier, and patients who had started treatment with a dopamine agonist had developed these treatment complications later. Although a satisfactory response to medication was associated with higher rates of motor complications, poor or moderate response was associated with lower quality of life in patients with a disease duration of ≤5 years or ≥10 years. We conclude that motor fluctuations are most strongly related to disease duration and dose of levodopa, and dyskinesias to duration of levodopa treatment. However, poorer quality of life associated with inadequate dosage of levodopa may be the price for a low rate of motor complications in patients with Parkinson's disease.

Keywords: Parkinson's disease; motor fluctuations; dyskinesias; levodopa

Introduction

The occurrence of dyskinesias and motor fluctuations is a major problem in the long-term management of patients with Parkinson's disease. It has been estimated that after initiation of treatment with levodopa, ~10% of patients per year develop motor fluctuations (Marsden and Parkes, 1977), and in clinic-based studies ~50% suffer these complications after 5 years of treatment (Sweet and McDowell, 1975; Dupont *et al.*, 1996). However, considerable controversy exists as to whether their occurrence is primarily related to the disease itself or to its treatment, and whether, as a consequence, treatment with levodopa should be delayed or kept at a low dose (Lees and Stern, 1981; Fahn and Bressman, 1984; Markham and Diamond, 1986; Melamed, 1986; Poewe *et al.*, 1986; Blin *et al.*, 1988; Roos *et al.*, 1990; Cedarbaum *et al.*, 1991; Montastruc *et al.*, 1999; Weiner, 1999). In animal studies the occurrence of motor complications is related to the degree of loss of dopaminergic neurones in the substantia nigra (Schneider, 1989; Boyce *et al.*, 1990*a*), and patients with MPTP (1-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine)-induced parkinsonism, who have severe depletion of nigral dopaminergic neurones (but are also young), develop motor complications rapidly and severely (Ballard *et al.*, 1985). However, the prevalence of motor complications in MPTP-treated animals also depends on the duration and dose of treatment with levodopa (Boyce *et al.*, 1990*b*; Arai *et al.*, 1996). In clinic-based samples of patients with Parkinson's disease, motor complications have been shown to occur more frequently and earlier in patients with younger onset (Kostic *et al.*, 1991), and to increase with longer disease duration and greater disease severity (Lesser *et al.*, 1979; Tanner *et al.*, 1985; Parkinson Study Group, 1996). It has also been claimed that dyskinesias occur more frequently in women if disease duration is >5 years (Parkinson Study Group, 1996; Lyons *et al.*, 1998). On the other hand, higher doses of levodopa (Barbeau, 1980; Lees and Stern, 1981; Tanner *et al.*, 1985) and longer duration of treatment (Miyawaki *et al.*, 1997) have been found to be associated with higher rates of these complications, and initiation of treatment with other antiparkinsonian drugs has resulted in lower rates or delayed appearance of motor fluctuations and dyskinesias (Lees and Stern, 1981; Rinne, 1987; Brannan and Yahr, 1995; Rascol

et al., 2000). However, many of these variables are related, such as age of onset, disease duration, duration of treatment, disease severity and dose of levodopa. It is therefore difficult to determine which of these factors are most important for the development of motor complications. In addition, clinic-based samples are probably not representative of the overall population of patients with Parkinson's disease. They may be biased towards more severely affected or younger patients, or those with a higher rate of complications. Patients seen in specialist neurological clinics are also more likely to be treated with high doses and more complex regimens of medication.

We therefore assessed the prevalence of motor fluctuations and dyskinesias in an unselected community-based sample of patients with Parkinson's disease, and investigated the influence of disease- and treatment-related variables on their occurrence.

Methods

One hundred and twenty-four patients, who were assessed in a prevalence study of parkinsonism with the primary aim of differentiating different types of parkinsonism (Schrag *et al.*, 1999), were examined and diagnosed with probable Parkinson's disease according to strict clinical diagnostic criteria (Gibb and Lees, 1989). Patients with multiple system atrophy and supranuclear palsy, vascular parkinsonism, drug-induced parkinsonism, and those with parkinsonism following dementia were excluded. The methods of patient ascertainment and study design were reported previously (Schrag *et al.*, 1999). In brief, the records of 15 general practices in the London area were screened for patients with a suspicion of Parkinson's disease or parkinsonism, for patients with tremor with onset after the age of 50 years, and for patients who had ever received antiparkinsonian drugs. As the health care system in the UK is organized locally, the population of a general practice is representative of the surrounding area. In addition, the general practitioner acts as a 'gatekeeper' of the National Health Service, so that patients are only referred to specialists by their general practitioners. Overall, 241 patients fulfilled screening criteria and participation prevalence was high (84%). Patients who had declined were slightly older than those who participated ($P < 0.05$), but there was no significant sex difference. Among the 202 patients who were seen, a diagnosis of probable Parkinson's disease was made in 124. This number differs from the number of patients with Parkinson's disease in the overall sample (Schrag *et al.*, 2000), which also included patients who could not be examined. The majority of patients had, on at least one occasion, seen a neurologist or a geriatrician with an interest in Parkinson's disease (92 patients, 74%).

All participating patients gave informed consent to participating in the study, which was approved by the Ethics Committee of the Institute of Neurology and National Hospital for Neurology and Neurosurgery, London. They had a semistructured general and neurological interview and examination, and clinical details were collected during the diagnostic visit. All patients were questioned about the presence of oscillations in motor response, i.e. predictable wearing-off, unpredictable on–off fluctuations and sudden off-periods, as defined in the Unified Parkinson's Disease Rating Scale (Fahn *et al.*, 1987), and involuntary movements (peak-dose, diphasic and off-period) related to treatment and their time of first occurrence. Six patients in whom dyskinesias were noticed during the 3-h examination but had not been reported by the patient or carer, were included in the group of patients with dyskinesias. Patients were also asked to complete a disease-specific quality of life instrument, the PDQ39 quality of life questionnaire, from which a summary index was calculated (Peto *et al.*, 1995). In addition to patient interview and examination, the general practitioners' records were examined for details of the patients' medical history and medication, including time of diagnosis and initiation of treatment, as well as documentation of patient complaints and clinical findings. If the dose of antiparkinsonian treatment listed in the records differed from that which the patient and carer reported as actually taken, the dose reported by the patient and carer was taken as the current dose.

Statistical analysis

The main analysis was performed on the subgroup of patients who had received levodopa, and consisted mainly of calculating rates and proportions. The dataset was examined to test the assumptions underlying parametric tests. Group differences were analysed by Student's *t*-test. Categorical data were compared with the χ^2-test, and Fisher's exact test if the numbers were small. Pearson correlations were calculated between variables. A statistical level of 5% was considered as significant in most analyses. However, in order to take into account multiple comparisons between patients with and without dyskinesias and motor fluctuations, a statistical threshold of $P < 0.005$ was considered to be sufficiently conservative for this analysis. Differences with $P > 0.005$ and $P < 0.1$ were considered as a trend. In order to determine which factors contribute most to the prediction of the occurrence of motor fluctuations and dyskinesias, we performed forward stepping logistic regression analyses, conducted using SPSS for Windows version 8.0. In these analyses, the presence or absence of dyskinesias or motor fluctuations were the dependent variables, and all variables that had differed between those with and those without complications at the 5% level were entered.

Results

Prevalence of motor fluctuations and dyskinesias

The characteristics of all patients receiving levodopa are given in Table 1. In the overall sample of patients with Parkinson's disease, 35 (29%) had experienced motor

Table 1 *Characteristics of Parkinson's disease patients on levodopa (*n = *87)*

	Mean	SD
Age (years)	71.3	11.6
Disease duration (years)	6.8	4.3
Age at onset (years)	64.5	7.3
Duration of treatmeant with levodopa (years)	5.2	4.4
Dose of levodopa (mg/day)	423.3	227.6
Hoehn and Yahr stage	2.4	0.8
Schwab and England score	81.3	15.1
PDQ39 score	28.8	18.3
Percentage of patients who were		
male	47.1	
on amantadine	5	
on selegiline	32.5	
on an anticholinergic	13	
on a dopamine agonist	14	

PDQ = quality of life questionnaire (Peto *et al.*, 1995).

fluctuations and 24 (19%) dyskinesias. Apart from one patient in whom levodopa had been discontinued due to psychiatric side-effects, all of these patients were currently taking a levodopa preparation. Among the patients who had received levodopa (n = 87, 70%), the rate of motor fluctuations was 40% and that of dyskinesias 28%. If only the patients who had an excellent or good response to levodopa (>50% improvement, subjective rating by patients and carers) were considered (n = 38, 44% of levodopa-treated patients), the rates were 50 and 29%, respectively. Among patients receiving doses of >300 mg levodopa per day (n = 44, 51% of levodopa-treated patients), the rates were 61 and 41%, respectively.

Prevalence of motor complications by disease duration, treatment duration and Hoehn and Yahr stage

The rates of occurrence of motor fluctuations and dyskinesias in levodopa-treated patients with a disease duration of 5 years or less were 14 and 7%, respectively. After a disease duration of 6–9 years they had occurred in 39 and 18%, respectively, and after 10 or more years of disease they had occurred in 67 and 57%. These rates were lower if the overall sample including patients not on levodopa was considered, and greater when only those who had a good or excellent response to levodopa, or those with levodopa doses of >300 mg were considered (Table 2).

After a treatment duration of 5 years or less, 21 and 13% of patients on levodopa had developed fluctuations and dyskinesias, respectively, after 6–9 years of treatment 56 and 36%, and after 10 or more years all patients had developed dyskinesias and motor fluctuations.

Motor complications had not occurred in patients on levodopa with a Hoehn and Yahr stage of 1 or 1.5 (as assessed during the diagnostic visit), but 42% of those in stages 2 or 2.5 had motor fluctuations and 29% had dyskinesias. In stage 3 patients, motor fluctuations were present in 50% and dyskinesias in 43%, and in patients in Hoehn and Yahr stages 4 or 5 they were present in 71% and 60%, respectively.

Subtypes of motor fluctuations and dyskinesias

Motor fluctuations were predominantly 'wearing off' fluctuations (n = 30, 34% of patients on levodopa), but nine (10%) patients had more severe on–off fluctuations, and six patients (7%) experienced sudden off-periods. Dyskinesias were predominantly peak dose (n = 22, 25%), but five patients (6%) had diphasic dyskinesias and nine (10%) off-period dystonia.

Wearing off had developed in 19% of patients treated for 5 years or less, 44% of those treated for 6–9 years, and 100% of those treated for 10 or more years, whereas unpredictable on–off fluctuations had not developed in any of the patients with a treatment duration of 5 years or less, and were present in 20% of those with a treatment duration of 6–9 years, and 50% of those with a treatment duration of 10 or more years. Sudden off-periods had occurred in 2, 8 and 33% of patients after treatment durations of five years or less, 6–9, and 10 or more years, respectively. Peak-dose dyskinesias were present in 11% of patients with a treatment duration of 5 years or less, 32% with a treatment duration of 6–9 years, and 89% of patients with a treatment duration of 10 or more years. Off-period dystonia was reported by 2, 12 and 56% of patients, respectively, and diphasic dyskinesias were reported by no patients with a disease duration of 5 years or less, and 4 and 44% of those with a disease duration of 6–9, and 10 or more years, respectively. Patients with diphasic dyskinesias and off-period dystonia as well as wearing-off fluctuations had a younger age at onset (all $P < 0.05$).

Time to onset of complications

The mean time from symptom onset to development of fluctuations, as reported by the patients, was 6.5 (SD = 4.1) years, and to development of dyskinesias 6.7 (SD = 3.1) years. The mean time from start of levodopa to the onset of fluctuations and dyskinesias was 4.8 (SD = 34) and 5.7 (SD = 2.7) years, respectively.

The latency from onset of symptoms to development of fluctuations and dyskinesias correlated positively with the time elapsed between onset and initiation of treatment with levodopa (r = 0.59, P = 0.02 and r = 0.54, P = 0.05, respectively). This could be due to a faster development of motor complications because levodopa was given earlier, but also to more rapidly progressive disease warranting earlier introduction of levodopa in some patients. The patients with more rapidly progressive disease would then be expected to be more severely disabled after the same duration of disease. Thus, disease severity should be negatively correlated with time from onset to initiation of levodopa, when controlled

Table 2 *Percentage of Parkinson's disease patients with motor fluctuations and dyskinesias by disease duration*

	Disease duration		
	⩽5 years	6–9 years	⩾10 years
Motor fluctuations			
Overall sample	8	27	63
Patients on levodopa	14	39	67
Patients with a good* response to levodopa	25	60	75
Dyskinesias			
Overall sample	4	12	53
Patients on levodopa	7	18	57
Patients with a good* response to levodopa	6	20	67

*Response >50%.

for disease duration. However, we did not find such a correlation ($r = 0.14$, $P = 0.2$), indicating that more rapidly progressive disease is not the explanation for the earlier development of motor complications in patients treated sooner with levodopa.

Time from onset to development of motor complications was also positively associated with current age ($r = 0.76$, $P = 0.004$ for dyskinesias, and $r = 0.30$, $P = 0.27$ for fluctuations), indicating that older patients develop dyskinesias later. Although greater age was also associated with lower doses of levodopa ($r = –0.30$, $P = 0.005$), age was still positively correlated with time from onset to development of dyskinesias after adjusting for levodopa dose ($r = 0.78$, $P = 0.005$ for dyskinesias and $r = 0.29$, $P = 0.3$ for fluctuations). Age at disease onset also correlated with time to onset of motor complications ($r = 0.82$, $P = 0.05$ for dyskinesias, $r = 0.25$, $P = 0.6$ for fluctuations). Thus, patients with younger age of onset tended to have dyskinesias earlier than those with greater age of onset.

Patients initially treated with a dopamine agonist

One patient was treated with a dopamine agonist alone and had not developed dyskinesias or motor fluctuations after a disease duration of 4.5 years. Three patients had received a dopamine agonist at the initiation of antiparkinsonian treatment, with levodopa added simultaneously or later. One of these patients had not developed motor complications after a disease duration of 2.9 years and a treatment duration of 2 years. The other two patients had developed motor fluctuations after a disease duration of 7.4 and 12.6 years, and a treatment duration of 7.2 and 10.8 years. They had developed dyskinesias after 3.2 and 12.8 years after onset of symptoms, and after 3 and 11 years of treatment. Thus, these patients had a longer delay from beginning of treatment to onset of motor fluctuations than those treated with levodopa from the beginning (8.6 versus 3.7 years, $P = 0.02$), and from onset of symptoms to first occurrence of motor fluctuations (10.3 versus 5.6 years, $P = 0.05$). Dyskinesias also occurred later after the start of treatment (7.0 versus 5.0 years) and after onset of symptoms (8.0 versus 6.0 years) in the patients who were started on a dopamine agonist than in those started on levodopa, but this difference did not reach statistical significance ($P = 0.26$ and $P = 0.32$, respectively). No such differences were seen between patients started on other antiparkinsonian drugs and those starting treatment with levodopa.

Differences between patients with and without motor fluctuations and dyskinesias

Patients with motor fluctuations had significantly longer disease duration, treatment duration, higher doses of levodopa, and tended to have longer time since diagnosis than those without. They also had greater disability, as measured by the Schwab and England scale, and tended to have greater disease severity, as measured by the Hoehn and Yahr scale, more often had a good response to levodopa, and were receiving a levodopa dose of >300 mg per day. They also tended more often to have a family history of parkinsonism in a first or second degree relative and to have the akinetic-rigid subtype of parkinsonism (Table 3). There was no difference in the use of antiparkinsonian medication other than levodopa, but this may have been due to the small number of patients with concomitant or alternative Parkinson's disease medication.

Patients with dyskinesias had a significantly longer treatment duration and were more severely disabled than those without. They tended to have longer disease duration, greater disease severity and to have received a higher levodopa dose, and more often reported falls than those without dyskinesias (Table 3). Men and women did not differ significantly with respect to the occurrence of motor fluctuations or dyskinesias, even when only those with a treatment duration of >5 years were considered. Age, symptom at onset, or time from onset to initiation of treatment did not differ between the groups.

Table 3 *Differences between patients with and without motor fluctuations and dyskinesias (mean/SD)*

	Motor fluctuations			Dyskinesias		
	With	Without	*P* value	With	Without	*P* value
Age (years)	68.8/10.2	73.3/12.2	0.09	70.0/11.3	71.8/11.7	0.6
Disease duration (years)	9.0/5.2	5.2/2.6	0.00004	8.8/5.8	5.9/3.5	0.01
Time since diagnosis (years)	7.2/4.7	4.3/4.1	0.03	7.4/3.8	5.0/4.8	0.13
Treatment with levodopa (years)	7.4/5.4	3.5/2.6	0.00006	7.5/6.0	4.2/3.4	0.005
Time from onset to initiation of levodopa (years)	0.5/0.8	1.5/1.5	0.5	0.5/3.8	1.7/2.3	0.6
Levodopa dose (mg/day)	542.3/224.1	340.4/191.8	0.00003	515.8/221.2	393.9/228.9	0.04
Hoehn and Yahr stage	2.6/0.7	2.2/0.7	0.006	2.7/0.7	2.3/0.7	0.04
Schwab and England score	73.8/18.3	86.2/10.1	0.002	72.6/17.6	84.7/12.9	0.001
Percentage of patients with						
levodopa dose >300 mg/day	79.4	20.6	0.0001	73.7	45.9	0.01
good response to levodopa	100	56.3	0.0003	100	65	0.05
family history of parkinsonism	39.3	11.1	0.05	43	20.2	0.09
akinetic-rigid subtype	94.7	53.5	0.02	90	71.2	0.4
falls	78.9	58.3	0.15	100	56.8	0.01

Logistic regression analysis

In order to understand the relationship of different variables to the occurrence of motor complications, we performed separate stepwise logistic regression analyses, taking dyskinesias and motor fluctuations as the target variables in each case.

Taking motor fluctuations as the dependent variable, the only variable included in the regression equation using this method of variable entry was disease duration. No other disease- or treatment-related factor was a significant predictor of the occurrence of motor fluctuations. In a separate hierarchical logistic regression analysis, treatment duration, levodopa dose, response to treatment, family history of Parkinson's disease, disease severity and disability were entered as a second block of variables after disease duration was entered as a covariate in the first block, but this set of variables did not increase the predictive power of the equation. In a series of separate hierarchical logistic regression analyses, these variables were then entered individually in the second block, after controlling for disease duration in the first block. The only variable that significantly increased the predictive power of the regression equation was dose of levodopa ($\chi^2 = 7.0$, $P = 0.008$). Using disease duration and dose of levodopa, 85% of patients without motor fluctuations were correctly classified, compared with 55% of the patients with motor fluctuations; on average, 72% of patients were categorized correctly. As such, this set of variables appears to be reasonably good at predicting the occurrence of motor fluctuations.

Using stepwise logistic regression with dyskinesias as the dependent variable, the only variable included in the regression equation was treatment duration. A correct classification of dyskinesias was possible in 88% (sensitivity 75, specificity 97%). When treatment duration was entered alone in the first block, no other variable increased the power of prediction further when entered in the second block either together or separately. When disease duration was entered in the first block of the analysis, no other variable entered individually was a significant predictor of the occurrence of dyskinesias. However, when all variables except disease duration were entered as a group in the second block of a hierarchical stepwise regression analysis, treatment duration significantly increased the power of the prediction of dyskinesias ($\chi^2 = 3.7$, $P = 0.05$). Thus, treatment duration appears to be related to the occurrence of dyskinesias over and above duration of disease.

Patients without motor complications after 10 or more years of disease

A subgroup of 10 levodopa-treated patients had not developed motor fluctuations even after a disease duration of 10 years, and 13 patients had not developed dyskinesias. Among patients with a disease duration of 10 or more years, those without fluctuations had a shorter disease duration than those with fluctuations ($P = 0.05$). Age, age at onset, treatment duration, Hoehn and Yahr stage, Schwab and England score, levodopa dose and sex were not significantly different between these patients and those who had developed motor complications.

Quality of life

Quality of life was not significantly different between patients with and without motor fluctuations and dyskinesias. However, when quality of life of patients was evaluated according to response to treatment (which was associated with higher doses of levodopa), it was significantly better in those with a good response to levodopa than in those with a moderate or poor response in those with a disease duration of 5 or less or 10 or more years (both $P < 0.05$).

Discussion

The prevalence of both fluctuations and dyskinesias increased with increasing disease and treatment duration as well as

advancing disease severity. Thus, no patient in Hoehn and Yahr stage 1 or 1.5 had any motor complications, whereas >70% of those in stages 4 or 5 had motor fluctuations and 60% dyskinesias. Similarly, after a disease duration of 10 or more years, >60% had motor fluctuations, and >50% dyskinesias.

These rates of motor complications are lower than rates of response fluctuations and dyskinesias in patients after the same disease and treatment durations in large clinic-based, cross-sectional (Cedarbaum *et al.*, 1991; Fahn, 1992; Miyawaki *et al.*, 1997) and longitudinal (Parkinson Study Group, 1996) studies. Patients in these studies, which may be biased towards younger subjects or those with more severe disease, also used higher mean doses of levodopa. To our knowledge, no comparable data are available on the rate of dyskinesias in an unselected population of patients with Parkinson's disease, and only one study has previously provided community-based data on the occurrence of motor fluctuations (Tandberg *et al.*, 1995). In that study, which also included patients not receiving levodopa, the rate of motor fluctuations was 21%, and in those classified as 'definite Parkinson's disease', who were required to have had a good response to levodopa, 28%. Although this prevalence is similar to our rate of 28% in the overall group of patients with Parkinson's disease, it is considerably lower than our rate in the subgroup of patients receiving levodopa, despite a higher mean dose of levodopa and longer mean disease and treatment duration in our study. Although there is no obvious explanation for this, it may be due to methodological differences in case ascertainment, diagnostic classification and a different definition of fluctuations, which was not specified further in the cited paper. In our study, we took great care even to include patients in the group with motor fluctuations who had noticed only mild wearing off.

It is generally believed that dyskinesias and motor fluctuations develop in ~50% of patients on treatment with levodopa after 5 years (Lang and Lozano, 1998), whereas the relationship of the occurrence of dyskinesias to duration of levodopa treatment is less clear (Fahn and Bressman, 1984). However, the rates of these complications on antiparkinsonian treatment reported in the literature vary greatly, ranging from 19 to 80% of patients experiencing fluctuations after 5 or 6 years of treatment with levodopa (Poewe *et al.*, 1986; Brannan and Yahr, 1995), and from 0 to 66% developing dyskinesias during the first year of treatment (Barbeau, 1980; Brannan and Yahr, 1995). A prospective study comparing standard release and controlled release levodopa/carbidopa (Block *et al.*, 1997) found fluctuations or dyskinesias in only 20% (patient rated) or 16% (observer rated) of patients after 5 years in either treatment arm, whereas another study comparing standard and sustained release levodopa/benserazide (Dupont *et al.*, 1996) found motor fluctuations in ~60% and dyskinesias in ~40% of patients after 5 years of treatment in both treatment arms. The DATATOP study, in which a large cohort of patients with Parkinson's disease were followed with regular appointments by movement disorder experts, also reported high rates of motor fluctuations and dyskinesias with ~50 and 30% of patients, respectively, developing these complications after treatment with levodopa for <2 years (Parkinson Study Group, 1996). The differences between these studies suggest that certain variables can influence the occurrence of motor fluctuations and dyskinesias on levodopa treatment. They have partly been attributed to different dosages of levodopa and the initial lack of use of peripheral decarboxylase inhibitor (Barbeau, 1980; Lees and Stern, 1981; Poewe *et al.*, 1986; Block *et al.*, 1997), as well as the prior or concomitant use of other medication, such as dopamine agonists (Rinne, 1987; Hely *et al.*, 1994; Montastruc *et al.*, 1994; Brannan and Yahr, 1995). Age at onset, age, sex, time from onset to initiation of levodopa and severity of disease may also influence the occurrence of dyskinesias (Pederzoli *et al.*, 1983; de Jong *et al.*, 1987; Blin *et al.*, 1988; Kostic *et al.*, 1991; Parkinson Study Group, 1996; Lyons *et al.*, 1998). In the present study we found that duration of disease and treatment as well as dose of levodopa were associated with a higher occurrence of motor complications, whereas age, sex and age at symptom onset were not different between those with and those without fluctuations or dyskinesias. However, younger patients and patients with younger age at onset had developed dyskinesias sooner than older patients or those with greater age at onset, whereas there was no significant correlation between time to onset of motor fluctuations and age or age at onset. Earlier treatment with levodopa was associated with earlier development of motor complications and, although numbers were small, treatment with a dopamine agonist was associated with a longer delay to the onset of motor fluctuations. This finding, in a community-based sample, supports the results of the recent large, double-blind and prospective studies that found a delay to the onset of motor complications in early Parkinson's disease in patients treated with dopamine agonists compared with those treated with levodopa alone. Thus, it was recently reported from a large, double-blind trial over 5 years that the risk of developing dyskinesias was substantially reduced in patients receiving the dopamine agonist ropinirole (if necessary complemented with levodopa), compared with those treated with levodopa from the outset (20 versus 45%, $P < 0.0001$; Rascol *et al.*, 2000). In another 3-year, double-blind study of the occurrence of motor complications in patients treated with pergolide compared with patients treated with levodopa, the 1-year interim analysis showed that the time to onset of motor complications was significantly longer with pergolide ($P = 0.038$; Hundemer *et al.*, 2000). Lower rates of motor complications compared with levodopa therapy were also seen in patients with early Parkinson's disease treated with the dopamine agonist pramipexole (with or without additional levodopa) for 2 years (28 versus 51%, $P < 0.0001$; Shoulson, 2000) and with cabergoline in a 5-year study (5 versus 32%, Musch *et al.*, 2000).

Patients with a positive family history of parkinsonism also tended to have motor complications more often than

those without. Although no other features were different between those with and without a family history of parkinsonism, this may indicate that a subgroup of patients with genetically determined parkinsonism has a higher propensity to develop these motor complications of treatment.

When we accounted for the interrelations of these disease- or treatment-related variables by using stepwise logisitic regression analysis, and entered all variables that differed between patients with and without motor complications, we found that disease duration and dose of levodopa were the best predictors for the occurrence of motor fluctuations. On the other hand, dyskinesias were best predicted by treatment duration alone. Age or symptom at onset, current age, sex or family history did not contribute further to the prediction of motor fluctuations or dyskinesias. However, the sensitivity of the prediction of dyskinesias was only slightly more than 50%, indicating that other variables, not identified in this study, have additional influence on their occurrence. The importance of treatment-related factors for the development of motor complications is supported by a number of further findings: (i) a shorter time from onset to treatment with levodopa was associated with earlier motor complications, which could not be adequately explained by more rapid disease progression; (ii) patients treated with a dopamine agonist from the outset developed motor complications later than those treated with levodopa alone; (iii) the prevalence of motor fluctuations and dyskinesias was lower than that reported in clinic-based samples receiving higher doses of levodopa after a similar disease duration (Dupont *et al.*, 1996; Parkinson Study Group, 1996; Miyawaki *et al.*, 1997); (iv) the rate of motor complications was higher in the subgroup of patients on levodopa than in the overall sample of patients with Parkinson's disease with the same disease duration (since no patient who had not received levodopa experienced these complications), and even greater in those patients who had a good response to levodopa or received >300 mg levodopa per day despite similar disease severity; (v) the difference in treatment duration between patients with and without dyskinesias was greater than the difference in disease duration. All these findings indicate that, although disease duration is an important factor in the development of motor complications, earlier and longer treatment with, as well as higher doses of levodopa are associated with a higher risk of dyskinesias. Our results are also similar to those in a recent, clinic-based study of patients with Parkinson's disease, in which longer treatment duration and shorter latency to initiation of levodopa treatment were identified as the main risk factors for motor fluctuations and dyskinesias (Denny and Behari, 1999).

However, it should also be noted that a large percentage (42% and 33%) of patients on levodopa without dyskinesias and fluctuations were not receiving doses sufficient to provide satisfactory benefit, and that those with unsatisfactory response to medication in the initial years of disease, as well as in later stages after 10 or more years of disease duration, had significantly worse quality of life than those with a good response to medication. Thus, although not experiencing motor complications, which were mild in the great majority of patients, these patients were failing to derive adequate benefit from medication, which resulted in poorer quality of life.

We believe that these results can be generalized to the overall population of patients with Parkinson's disease, as we evaluated an unselected sample, and endeavoured to achieve high diagnostic accuracy, which was the primary aim of the study (Schrag *et al.*, 1999). However, as this was a cross-sectional assessment rather than a longitudinal follow-up study, it has two main limitations: first, the drug treatment of patients was not adjusted in a uniform way as they were under the care of many different clinicians, and secondly and most importantly, most of the information was reported retrospectively by the patients themselves or derived from the records of their general practitioners. In particular, patients were not examined before the start of treatment, the time of onset of complications was reported by the patients themselves and their carers, and the majority of patients were only assessed on one or two occasions. In six cases, dyskinesias were noticed by the examiner, but were not reported by the patients or carers. It is thus possible that the frequency of motor fluctuations or mild dyskinesias in this cross-sectional study may thus have been underestimated, and that the onset of these complications might have occurred earlier than reported.

In summary, we found that, among patients treated with levodopa, response fluctuations and dyskinesias had developed in ~40 and 30%, respectively. These rates increased with disease duration and severity, but they were also strongly related to treatment-related factors, such as duration and dose of levodopa. Earlier treatment with levodopa as well as younger age were associated with earlier development of motor complications, and initial treatment with a dopamine agonist, in a small number of patients, was associated with a later onset of motor complications. However, less effective treatment and poorer quality of life associated with inadequate dosage of levodopa may be the price to pay for a low rate of motor complications in patients with Parkinson's disease.

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