Patterns of levodopa response in Parkinson’s disease: a clinico-pathological study

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Patients with Parkinson’s disease who develop disabling levodopa-induced motor fluctuations have a stronger therapeutic response than those who experience a more modest but stable response. A difference in the histopathological lesion between the two groups might be responsible. Case records from 97 patients with pathologically proven Parkinson’s disease were reviewed to determine the pattern of levodopa response. Pathological findings for fluctuating and non-fluctuating cases were compared. Patients with motor fluctuations had a younger age of onset and longer disease course (P < 0.001), although mean age at death was almost the same. Four milestones of advanced disease (frequent falls, visual hallucinations, cognitive disability and need for residential care) occurred at a similar time from death in each group; this interval was not proportionate to the disease duration. There were no significant differences in the severity or distribution of Lewy body or other pathologies. Irrespective of the pattern of levodopa response, patients reach a common pathological endpoint at a similar age, and the duration and manifestations of end-stage disease are alike. A non-linear or exponential time relationship may govern the late clinical and pathological progression of Parkinson’s disease.

Keywords: Parkinson’s disease; motor fluctuations; Lewy body

Abbreviations: LB = Lewy body


Introduction

The pattern of response to pharmacological treatment has important influences on the course of Parkinson’s disease. Some patients respond rapidly and strikingly when levodopa is started, while others obtain only a modest benefit. A good initial response usually predicts motor fluctuations and dyskinesias. There are some patients who never describe motor fluctuations, despite a progressive increase in motor handicap. Surveys of the prevalence of fluctuations estimate that between 41 and 83% are eventually affected (Ahlskog and Munter, 2001). In a retrospective study of pathologically proven Parkinson’s disease, 52% had motor fluctuations recorded in the case notes (Rajput et al., 2002).

It is well established that the magnitude of response to levodopa test doses (i.e. the short duration levodopa response) is the critical factor determining if patients will notice and report motor fluctuation related to levodopa medication (Nutt et al., 1992; Contin et al., 1993; Hughes et al., 1994, McColl et al., 2002). Those who are treated with levodopa and have not developed fluctuations later in the disease course have smaller, but not negligible, responses (Clissold et al., 2006). Non-fluctuators often have earlier and more severe axial and bulbar impairment (McColl et al., 2002). These different patterns of response must reflect pathological or neurochemical differences, some of which may be age-related. Strongly responsive patients who fluctuate are likely to have severe loss of dopaminergic nigral neurons with other parts of the motor system, including the post-synaptic striatal dopamine receptors, relatively intact. Poorer responses might be expected when extranigral pathology, Lewy body-related or otherwise, causes damage to the effector systems for dopamine receptor stimulating treatment.

In this study, we have recorded the presence and severity of motor fluctuations as a guide to the degree of levodopa
responsiveness and sought clinico-pathological correlation with the pattern of the levodopa response.

**Material and Methods**

**Patients**

Patients with an initial clinical diagnosis of parkinsonism and a pathologically proven diagnosis of Parkinson’s disease were identified from the records of donors to the Queen Square Brain Bank for Neurological Disorders that were autopsied between 2001 and 2006. Patients with a primary initial diagnosis of dementia were excluded. Eligible cases were first identified from the register of the summarized clinical details and pathological reports, which contained information on 384 brain donors. The definition of the pathological diagnosis of Parkinson’s disease was depletion of neurons in the substantia nigra pars compacta associated with Lewy bodies. The London Multi-Centre Research Ethics Committee has approved procedures for the donation of brains to the Queen Square Brain Bank as well as retention of and access to clinical records.

**Medical record review**

We performed a systematic review of the case files. All patients had been assessed by hospital specialists (neurologists or geriatricians). Cases were excluded if the medical records did not contain regular and well-documented reports of clinical developments and pharmacological treatment. The onset of Parkinson’s disease was defined as the time of diagnosis, not the retrospective report of first symptoms. Levodopa-containing medication had to have been used for >50% of the disease course and, once started, continued in some form until the terminal phase of the illness.

The year of onset of motor fluctuations and their maximum subsequent severity was recorded. Because of the management implications of a fluctuating motor response, its documentation was usually extensive. Motor fluctuations were graded as follows: mild—symptomatic wearing off effects not causing significant change in functional motor status; moderate—alterations in motor performance which interfered with tasks of daily living, and required adjustment of treatment on at least one occasion; severe—on-off fluctuations with incapacitating off phase disability. The year of onset of dyskinesia and the maximum levodopa dose were determined.

Four milestones of disease advancement were selected on the basis that each was likely to require additional medical attention and to be well recorded in the dossier. These were: frequent falling, visual hallucinations, cognitive disability and placement in residential care. The year of onset or occurrence of each was recorded. The judgement about onset of cognitive disability was the most difficult to make as confusion was often initially episodic. Substantial and apparently permanent impairment of ability to perform tasks of daily living because of cognitive disability was the criterion used [DSM-IV (1995)] (severity criterion for dementia). The first recording of visual hallucinations and falling was taken as the time of onset. The fact that the symptoms often commenced some time before a clinic visit may have reduced the accuracy of these determinations.

**Pathological studies**

Previously described methods were used for fixation, sectioning and staining of brain tissue (Colosimo et al., 2002). Sections were immunostained with polyclonal anti-alpha synuclein antibodies (Novocastra). The Consensus Guidelines for Pathological Diagnosis of Dementia with Lewy Bodies (McKeith et al., 1996) were used to measure Lewy body (LB) distribution and severity. Sections of transentorhinal and cingulated cortex and three neocortical areas (second frontal gyrus, superior temporal gyrus and inferior parietal cortex) were examined. A semi-quantitative scale was used to derive a LB score for each area, summated to give a final score. Total scores of 7–10 were classified as neocortical LB disease.

**Statistical analysis**

Clinical details including age at disease onset, age at death, disease duration and maximum levodopa dose were compared between fluctuators and non-fluctuators. Mean results and comparisons for each milestone of advanced disease refer only to those patients in whom one of these event occurred. The severity of LB pathology, prevalence of additional pathologies and severity of Alzheimer pathology was also compared between groups. Univariable analyses using χ² for categorical and two-tailed t-test or the Mann–Whitney U-test, as appropriate, for continuous variables were applied. Mean ± SD shown in text and tables.

**Results**

Of 118 potential cases, 21 were excluded because of insufficient clinical documentation (15) or short duration of levodopa treatment (6). Perceived lack of response to levodopa and drug withdrawal was the reason for the short duration of levodopa treatment in 5 of these patients; 3 were misdiagnosed as progressive supranuclear palsy and 1 as corticobasal degeneration. There remained 97 patients who had received long-term levodopa therapy and had good records of their response pattern (65 men and 32 women; mean age at diagnosis 61.7 ± 10.3 years, range 43–80 years).

Sixty-two patients (64%) eventually developed some motor fluctuation (17 mild, 26 moderate and 19 severe). Thirty-five patients were classified as non-fluctuators. The most difficult judgement concerned those patients who were modestly responsive to medication and eventually developed some mild fluctuations late in the disease course. More substantial motor fluctuations generally evolved clearly, although the distinction between moderate and severe was sometimes blurred. In light of this, it was decided to group moderate and severe gradings together for the main statistical comparisons between clearly fluctuating and non-fluctuating patients. The demographic and clinical data according to fluctuation status is shown in Table 1.

Age at death was similar in each group. The disease course was significantly longer and the age of onset significantly younger in moderate and severe fluctuators compared to non-fluctuators (P<0.001). Most patients died from the effects of advanced Parkinson’s disease or
from other medical disorders while already severely disabled by Parkinson's disease. However, there were nine cases where death was premature. Causes of death in these cases were neoplasm (4), cardiovascular disease (3) and cerebrovascular disease (2); they were evenly distributed across the motor response subgroups (non-fluctuators 4, mild 1, moderate–severe 4).

Levodopa treatment was initiated at the time of diagnosis in 53 cases (54%). The remainder started treatment after a mean period of 1.9 (range 1–6) years. There was no significant difference in the time to commencement of levodopa between non-fluctuators and moderate-severe fluctuators. Moderate-severe fluctuators took significantly higher maximum levodopa dosage ($P < 0.001$). Mean time to maximum levodopa dose was 8.3 (range 1–23) years.

Oral dopamine receptor agonists (bromocriptine, pergolide, lisuride, cabergoline, ropinirole) were used in 35% of the patients. The difference between moderate-severe fluctuators (40%) and non-fluctuators (31%) was not significant. Dopamine receptor agonist treatment was started before levodopa in only two cases. Apomorphine was administered subcutaneously, by intermittent injection or by continuous infusion, to 18 patients; all had motor fluctuations (14 severe, 4 moderate). Thirty-nine percent were given slow release levodopa medications, with no difference between moderate-severe fluctuators and non-fluctuators. Other drugs were used as follows: deprenyl 13%, amantidine 8%, COMT inhibitor agents 5%, anticholinergics 4%.

Dyskinesia was recorded in 14% of non-fluctuators, the majority of mild fluctuators and all but two of the moderate–severe group (both graded as moderate).

Table 2 shows the milestones of advanced disease for each group. There were no significant differences between the fluctuators (moderate and severe) and non-fluctuators for incidence of milestones or interval to death. In 76% of cognitively disabled cases, visual hallucinations were recorded. Only two patients developed cognitive disability before the age of 65 years. Figure 1 shows that the advanced disease milestones develop with a constant temporal relationship at the end of the disease, which is determined by the age of the patient not the duration of motor symptoms. Fifteen cases had no recorded advanced disease milestones. They were evenly distributed across fluctuation groupings; their mean disease duration (10.2 years; range 3–19) was shorter than the mean for all patients (14.0 years), and reflected the presence of a number of the premature deaths from intercurrent medical disorders in this group.

Clinico-pathological analysis

There were no significant differences in the incidence or severity of pathology across the groups. Details are summarized in Table 3. All cases showed moderate or

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**Table 1 Clinical features**

<table>
<thead>
<tr>
<th></th>
<th>Non-fluctuators</th>
<th>Mild fluctuators</th>
<th>Moderate-severe fluctuators</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>35 (36)</td>
<td>17 (18)</td>
<td>45 (46)</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>6 (17)</td>
<td>6 (35)</td>
<td>20 (44)</td>
<td></td>
</tr>
<tr>
<td>Mean age at diagnosis (years)</td>
<td>$66.4 \pm 8.3$</td>
<td>$61.3 \pm 9.6$</td>
<td>$579 \pm 10.7$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean disease duration (years)</td>
<td>$99 \pm 6.4$</td>
<td>$130 \pm 4.2$</td>
<td>$176 \pm 5.9$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean age at death (years)</td>
<td>$76.3 \pm 8.3$</td>
<td>$74.4 \pm 8.9$</td>
<td>$75.4 \pm 9.4$</td>
<td></td>
</tr>
<tr>
<td>Fluctuations – mean year of onset (range)</td>
<td>N/A</td>
<td>8.8 (2–20)</td>
<td>71 (1–23)</td>
<td></td>
</tr>
<tr>
<td>Dyskinesia – number (%)</td>
<td>5 (14)</td>
<td>12 (70)</td>
<td>43 (96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyskinesia – mean year of onset (range)</td>
<td>11.4 (6–17)</td>
<td>7.7 (1–20)</td>
<td>6.7 (1–15)</td>
<td>0.14</td>
</tr>
<tr>
<td>Maximum levodopa dosage (mg)</td>
<td>549 ± 267</td>
<td>665 ± 196</td>
<td>1041 ± 450</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Note:** Statistical comparisons for non-fluctuators versus moderate-severe fluctuators (ns—not significant).

**Table 2 Milestones of disease advancement**

<table>
<thead>
<tr>
<th></th>
<th>Non-fluctuators</th>
<th>Mild fluctuators</th>
<th>Moderate-severe fluctuators</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent falls Number (%)</td>
<td>11 (31)</td>
<td>5 (29)</td>
<td>16 (36)</td>
<td>ns</td>
</tr>
<tr>
<td>Frequent falls Mean years to death (range)</td>
<td>3.6 (0.2–14)</td>
<td>2.8 (0.6–5)</td>
<td>3.9 (1–8)</td>
<td>ns</td>
</tr>
<tr>
<td>Visual hallucinations Number (%)</td>
<td>18 (57)</td>
<td>10 (58)</td>
<td>29 (64)</td>
<td>ns</td>
</tr>
<tr>
<td>Visual hallucinations Mean years to death (range)</td>
<td>3.9 (1–9)</td>
<td>4.6 (2–8)</td>
<td>4.5 (1–12)</td>
<td>ns</td>
</tr>
<tr>
<td>Cognitive disability Number (%)</td>
<td>22 (63)</td>
<td>8 (47)</td>
<td>24 (53)</td>
<td>ns</td>
</tr>
<tr>
<td>Cognitive disability Mean years to death (range)</td>
<td>3.0 (1–8)</td>
<td>1.6 (0.7–4)</td>
<td>3.2 (0.6–8)</td>
<td>ns</td>
</tr>
<tr>
<td>Residential care Number (%)</td>
<td>22 (63)</td>
<td>8 (47)</td>
<td>20 (44)</td>
<td>ns</td>
</tr>
<tr>
<td>Residential care Mean years to death (range)</td>
<td>2.5 (0.2–6)</td>
<td>2.9 (0.6–8)</td>
<td>2.9 (0.8–7)</td>
<td>ns</td>
</tr>
</tbody>
</table>

**Note:** Statistical comparisons for non-fluctuators versus moderate-severe fluctuators.
severe neuronal loss in the substantia nigra associated with Lewy bodies. Neocortical Lewy body disease was present in 67%. Mean regional LB scores and numbers of cases affected by neocortical LB disease were similar in each group. There were five patients who were aged 55 years or younger at the time of death. They were evenly distributed across the fluctuator groupings. Their mean LB score was 5.0 compared with 7.7 for the older patients, although this difference was not significant and the mean disease duration for the younger group was relatively short at 7.2 years (range 3–15).

Alzheimer pathology was reported in 52 cases. These changes were generally of moderate severity. Mean Braak and Braak grading (Braak and Braak, 1991) was 2.5, with no significant differences between groups. Only two cases (both demented) conformed to CERAD criteria (Mirra et al., 1991) for a pathological diagnosis of definite Alzheimer’s disease (one non-fluctuator and one moderate/severe fluctuator). Pathologically significant changes of cerebrovascular disease and cerebral amyloid angiopathy were distributed evenly across the groups.

**Discussion**

Irrespective of the pattern of response to levodopa in life, patients with Parkinson’s disease reach a similar pathological endpoint. No significant differences could be discerned in the severity of LB pathology or other pathologies. If there are differences in pathology that determine whether patients respond strongly or weakly to levodopa during the course of the disease, they are no longer detectable at post-mortem examination. The major difference between the fluctuator and non-fluctuator groups was in the duration of the disease. Patients who had moderate or severe motor fluctuations were significantly younger at diagnosis and had a significantly longer disease course. This would be consistent with a slower rate of disease progression. Visual hallucinations, cognitive disability, regular falls and need for residential care marked the mental and physical decline of the final phase of the disease. Intriguingly, the time from these milestones to death was not significantly different for fluctuators and non-fluctuators, and did not appear to be proportionate to the length of the disease course.

Patterns of levodopa response have not previously been compared in a large clinico-pathological series. There have been a number of pathological studies correlated with the clinical features of advanced disease. Jellinger et al. (2002) found that the severity of neuritic plaque Alzheimer pathology was correlated with dementia, later age of onset, shorter disease course and akinetic-rigid motor sub-type. Braak et al. (2005) reported that staging based on the distribution of Lewy bodies and Lewy neurites was the most important determinant of cognitive impairment. Cognitively impaired patients also displayed higher stages of Alzheimer pathology, but the average additional Alzheimer disease burden was relatively low. The relationship between dementia and neocortical LB disease is not a

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**Table 3** Pathological results according to fluctuator classification

<table>
<thead>
<tr>
<th></th>
<th>Non fluctuators</th>
<th>Mild fluctuators</th>
<th>Moderate-severe fluctuators</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median LB score</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>ns</td>
</tr>
<tr>
<td>Neocortical LB disease number (%)</td>
<td>24 (69)</td>
<td>10 (59)</td>
<td>31 (69)</td>
<td>ns</td>
</tr>
<tr>
<td>Alzheimer changes number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean Braak &amp; Braak grade</td>
<td>19/35 (54)</td>
<td>9/17 (53)</td>
<td>24/45 (53)</td>
<td>ns</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy number (%)</td>
<td>2.7</td>
<td>2.0</td>
<td>2.5</td>
<td>ns</td>
</tr>
<tr>
<td>Cerebrovascular disease number (%)</td>
<td>7 (20)</td>
<td>1 (6)</td>
<td>9 (20)</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Note: Statistical comparisons for non-fluctuators versus moderate–severe fluctuators.*
constant one, and extensive cortical Lewy bodies are not always associated with severe cognitive decline (Colosimo et al., 2002; Braak et al., 2005). In our case review, cognitive disability was present in a similar percentage of the fluctuating and non-fluctuating groups. Lewy body deposition was the dominant cortical pathology; Alzheimer pathology was mild in most of the cases where it was observed. Our figures on visual hallucinations and their relationship to cognitive decline are similar to a survey of earlier cases also from the Queen Square brain bank (Williams and Lees, 2005). Allowing for differences in definition of falling and frequent falls, our findings are in line with previous clinical research (Balash et al., 2005; Wielinski et al., 2005).

Bradykinesia is the cardinal motor deficit in Parkinson’s disease and the chief source of disability for much of the disease course. It correlates with nigral cell loss (Greffard et al., 2006). PET studies show that the resultant striatal dopamine deficiency correlates with measures for bradykinesia in the UPDRS Part 3 scale (Lee et al., 1994). The effectiveness of dopamine replacement determines the levodopa motor response, and its variations produce motor fluctuations. However, the emergence of non-dopaminergic neural degeneration is responsible for many of the manifestations of the late disease phase. Hallucinations and dementia, which generally occurred together, can be largely attributed to neocortical Lewy body pathology. Both physical and cognitive disability contribute to the need for residential care, although Goetz and Stebbings (1993) identified the presence of hallucinations and delusions as the strongest risk factor for nursing home placement. Frequent falling is part of the motor disability, and is related to increasing difficulty with axial muscle control. Gait and balance deficits are more severe in older subjects despite optimum levodopa treatment, suggesting that non-dopaminergic lesions play a part in the falling tendency of late Parkinson’s disease (Blin et al., 1991). Cognitive impairment is also an independent predictor of falling (Wood et al., 2002).

Degenerative neurological disorders, whether they progress rapidly or slowly, usually give the clinical impression of a linear time course. In Parkinson’s disease, the effects of pharmacological treatment make it harder to perceive changes in the underlying condition, although follow up studies over 6 (Jankovic and Kapadia, 2001) and 8 (Alves et al., 2005) years produced linear plots of motor impairment against time. Our findings on the uniform duration of the advanced disease state could indicate that a non-linear or exponential time relationship governs the final, predominantly non-dopaminergic phase of the disease. One small but sustained longitudinal study of the levodopa motor response suggests something similar: serial motor impairment scores showed an exponential deterioration after the first decade of levodopa treatment (Clissold et al., 2006). In a subgroup of patients who had developed cognitive decline, this upward curving was more pronounced, and appeared to show a late phase of parallel acceleration of motor and cognitive impairment. In our study, the patient groups reached a common pathological endpoint at a similar average age, irrespective of the pattern of levodopa response, age of onset or disease duration, implying that age has a major influence on the dynamics of the spread of pathology. Jankovic and Kapadia have shown an age-related effect on the rate of worsening of motor scores (Jankovic and Kapadia, 2001). Age has previously been shown to be an independent risk factor for the development of falls (Williams et al., 2006), cognitive dysfunction (Levy et al., 2000) and visual hallucinations (Williams and Lees, 2005) in Parkinson’s disease, supporting the notion that in advanced age, brain pathology advances faster. Recent work on the staging of LB pathology hypothesizes that progression occurs as LB pathology spreads upwards from the lower brainstem and eventually involves the neocortex (Braak et al., 2003). Little information about the topographic stages of disease evolution can be inferred from our end-stage pathological data, but our observations on the milestones of advanced disease do question an assumption of the Braak staging system: its linear progression (Braak et al., 2006). If pathology progressed at a steady rate from Braak Stage 3 (the threshold of clinical disease) to Braak Stage 6 (severe neocortical involvement), one would expect to see that the time to advanced disease milestones was proportionate to the total disease duration. It is possible that spread of Lewy body pathology to the neocortex, because of involvement of additional neural systems and a much greater number of neurons, can produce exponential clinical effects. However, Halliday et al. (2006) have observed that the age distribution of early and late Braak stage pathology does not fit with simple linear age dependence.

The time to appearance of motor fluctuation and dyskinesia was longer than in some other surveys (Schrag and Quinn, 2000; Ahlskog and Muenter, 2001). One limitation of the retrospective assessment of case notes is that these phenomena may not have been recorded until they had become fully developed and were impacting on the patient’s quality of life. The prevalence of both fluctuations and dyskinesias was comparable with previous studies (Ahlskog and Muenter, 2001). The maximum dose of levodopa was significantly higher in fluctuating patients. The levodopa dosage was generally increased to counter motor fluctuations once they had developed, with more tablet doses, shorter inter-dose intervals and use of slow release levodopa preparations, but our retrospective analysis does not exclude the possibility that higher levodopa doses contributed to fluctuation severity. It is clear that non-fluctuating patients also took therapeutic dosages of levodopa over long periods, and that lack of fluctuation was unlikely to have been caused by insufficient exposure to levodopa.

Longitudinal clinical research and clinico-pathological studies like this one give a long-term perspective of the
References


