

A clinico-pathological study of subtypes in Parkinson's disease

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We have carried out a systematic review of the case files of 242 donors with pathologically verified Parkinson's disease at the Queen Square Brain Bank for Neurological Disorders in an attempt to corroborate the data-driven subtype classification proposed by Lewis and colleagues (Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. *J Neurol Neurosurg Psychiatry* 2005; 76: 343–8). Cases were segregated into earlier disease onset (25%), tremor dominant (31%), non-tremor dominant (36%) and rapid disease progression without dementia (8%) subgroups. We found a strong association between a non-tremor dominant disease pattern and cognitive disability. The earlier disease onset group had the longest duration to death, and greatest delay to the onset of falls and cognitive decline. Patients with a tremor dominant disease pattern did not live significantly longer than non-tremor dominant patients and showed no difference in mean time to onset of falls and hallucinations. Rapid disease progression was associated with older age, early depression and early midline motor symptoms, and in 70% of the cases, tremulous onset. The non-tremor dominant subgroup had a significantly higher mean pathological grading of cortical Lewy bodies than all other groupings ($P < 0.05$) and more cortical amyloid- β plaque load and cerebral amyloid angiopathy than early disease onset and tremor dominant groups ($P = 0.047$). An analysis of cases with pathologically defined neocortical Lewy body disease confirmed the link between bradykinetic onset, cognitive decline and Lewy body deposition in the neocortex. Although neuropathological examination failed to distinguish the other subtypes, the classification scheme was supported by an analysis of clinical data that were independent of the basic subgroup definitions.

Keywords: bradykinesia; Parkinson's disease dementia; Lewy body; tremor dominant phenotype; age of onset

Abbreviations: EDO = earlier disease onset; NTD = non-tremor dominant; QSBB = Queen Square Brain Bank; RDP = rapid disease progression without dementia; TD = tremor dominant

Introduction

The clinical heterogeneity of Parkinson's disease is well recognized (Hoehn and Yahr, 1967) and a number of proposals to divide patients into benign or malignant, tremor dominant and

predominantly axial forms have been published (Paulus and Jellinger, 1991; Brooks, 2000; Lees *et al.*, 2000; Francis and Perry, 2007; Spiegel *et al.*, 2007). It is generally agreed that there is a relatively benign tremulous form of the disorder. Although post mortem studies are limited, these patients appear

to progress slowly despite a poorer therapeutic response to levodopa. Early postural instability and gait involvement has been claimed to be associated with a worse prognosis for motor and cognitive function, but pathological confirmation of the diagnosis has been lacking in almost all published studies. When autopsies have been performed, some of these patients turn out to have multiple system atrophy or progressive supranuclear palsy-Parkinsonism (Marijama-Lyons and Koller, 2000; Lyros *et al.*, 2008; Post *et al.*, 2008).

Most Parkinson's disease phenotype studies have used methodologies that divide patients according to predetermined notions, leading to an inherent bias in their conclusions. A data-driven analysis without assumptions about the defining clinical features can help to minimize this effect. Two studies have used a cluster analysis of clinical data to segregate patients into subtypes. Graham and Sagar divided patients into 'motor only', 'motor and cognitive', and 'rapidly progressive' groups (Graham and Sagar, 1999). Lewis and colleagues concentrated on the early phase of the disease and their analysis favoured four subgroups: (i) younger disease onset; (ii) tremor dominant; (iii) non-tremor dominant with cognitive impairment; and (iv) rapid motor progression without cognitive impairment (Lewis *et al.*, 2005). In both studies, the subgrouping resulted in some discrimination at the time of diagnosis, whilst other definitions could only be satisfied after a number of years of disease progression. Even when stringent diagnostic criteria are used, clinically based phenotyping studies are prone to confounding effects from alternative or mixed neuropathology (Tsuboi and Dickson, 2005; Uchikado *et al.*, 2006).

Clinical separation into postural instability/gait difficulty and tremor dominant types has been the most extensively studied (Zetusky *et al.*, 1985; Doder *et al.*, 2003; Burn *et al.*, 2006). One previous clinico-pathological evaluation of subgroups found that postural instability/gait difficulty onset was present in 16%, and tremor dominant onset in 49% of all patients autopsied (Rajput *et al.*, 1993). Other studies have concentrated on cardinal motor signs, patterns of cognitive function and presence of depression (Louis *et al.*, 1999; Schiess *et al.*, 2000; Selikhova *et al.*, 2004). Gibb and Lees found that early onset (<45 years) patients presented more often with muscle stiffness and limb dystonia whereas old onset patients (>70 years) more often presented with gait difficulties and rest tremor. Despite a 12 year longer history at death, the only difference in the pathological lesion in the two groups was that the early onset group had 24% greater nigral cell loss (Gibb and Lees, 1988a).

In an attempt to verify two data-driven subgroup classifications, as proposed by Lewis and colleagues (2005) and Graham and Sagar (1999), we have taken advantage of the database at the Queen Square Brain Bank for Neurological Disorders (QSBB), where clinical records for the entire disease course were available for a substantial number of pathologically confirmed patients.

Patients and methods

Patients with a pathologically proven diagnosis of Parkinson's disease were identified from the records of donors to the QSBB who had been

autopsied between 1990 and 2006. Patients with a primary initial diagnosis of dementia were excluded (dementia at the time of diagnosis of Parkinson's disease or within 2 years of first symptoms). The London Multi-Centre Research Ethics Committee has approved procedures for the donation of brains to the QSBB as well as retention of and access to clinical records. Tissue is stored at the QSBB under a licence from the Human Tissue Authority. All brains had genetic screening. Three cases had LRRK2 mutations, but no Parkin mutations were found.

Medical record review

We performed a systematic review of the case files. All patients had been assessed by UK 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. Clinical notes were assessed by neurologists who specialize in movement disorders (M.S., D.W. and P.K.) and a sample of 10% (25 cases) were examined together to ensure good agreement between assessors.

The time point of the diagnosis of Parkinson's disease was established in each case, as well as the duration of symptoms at diagnosis. Disease onset was defined as the time of first recalled motor symptoms. The pattern of motor deficits (tremor, bradykinesia and rigidity) in the pre-treatment phase of the disease was determined from clinical records that were made at the time of diagnosis. A semi-quantitative scale (0—absent, 1—mild, 2—moderate, 3—severe) was applied to each physical sign. The presence of 'midline' motor symptoms or signs (affecting speech, swallowing, truncal mobility, gait or balance) at the time of diagnosis was recorded. If frequent falling developed later in the disease course, its timing was noted. Hoehn and Yahr staging of motor disability was recorded in 110 patients; in the remainder, an estimated Hoehn & Yahr (H&Y) score was derived from clinical descriptions referring to bilateral motor involvement, postural instability, use of walking aids or wheelchair and confinement to bed. The H&Y scoring was determined at the time of diagnosis and at 5, 8, 10 and 15 years into the disease course, and refers to the best motor function on treatment.

The time when levodopa was started and the maximum levodopa dose were registered. The presence and severity of dyskinesias and motor fluctuations was graded on a similar four-point semi-quantitative scale at the following time points: initial 1–2, 5, 8, 10 and 15 years.

The occurrence and time of onset of the following non-motor clinical features were recorded: (i) dementia, defined as substantial and permanent impairment of ability to perform tasks of daily living because of cognitive disability (Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV severity criterion for dementia); a documented Folstein mini-mental state examination score of <24 was taken as corroborative evidence; (ii) symptoms indicative of cognitive dysfunction at the time of diagnosis; (iii) clinically diagnosed depression, both before and after diagnosis; depression was graded as 1—none, 2—dysthymia, 3—mild, 4—severe; (iv) visual hallucinations; and (v) placement in residential care.

Subtype definitions

These definitions were designed to correspond as closely as possible to the Lewis subtypes within the practical constraints of retrospective, non-standardized data collection (Lewis *et al.*, 2005). The Lewis study principle of assigning all cases to a subtype was followed. Medical records pertaining to the first 5 years of the disease were

evaluated for the classification of motor features, but the documentation at the time of diagnosis was usually the most informative, and was given the greatest importance. Where both rest tremor and bradykinesia were present at the time of diagnosis, a judgement was made as to which was the more prominent.

The subgroups were defined as follows:

- (1) Earlier disease onset (EDO): below age of 55 years at disease onset.
- (2) Tremor dominant (TD): aged 55 years and over at onset; rest tremor as sole initial symptom or sustained dominance of tremor over bradykinesia and rigidity.
- (3) Non-tremor dominant (NTD): aged 55 years and over at onset; predominantly bradykinetic motor features with no or only mild rest tremor.
- (4) Rapid disease progression without dementia (RDP): death within 10 years from first Parkinson's disease symptoms, irrespective of age; no dementia, but progression to advanced motor disability by estimated or documented H&Y stage. Patients who had died prematurely of an unrelated medical disorder were not included in this category.

The classification was performed in two steps. Subtyping according to the clinical features of the early disease phase segregated cases into Groups 1–3. The RDP definition was then applied, taking precedence over the other definitions, and resulting in a four-subtype analysis.

To look for correlations with other subtyping systems, separate analyses were done to incorporate postural instability/gait difficulty, and to resolve the previously described 'motor and cognitive' phenotype (Zetuský *et al.*, 1985; Graham and Sagar, 1999; Doder *et al.*, 2003; Burn *et al.*, 2006). Clinical features of patients with early 'midline' motor deficits were compared with those patients without these features at diagnosis. The Graham and Sagar motor and cognitive grouping was defined by the presence of dementia within seven years of disease onset (Graham and Sagar, 1999). These patients with early dementia were compared with all other patients and their classification according to the Lewis subtype grouping was analysed.

Young onset Parkinson's disease is usually defined as age at onset between 21 and 40 years (Quinn *et al.*, 1987, Schrag *et al.*, 1998) and so the EDO subgroup was further segregated to study these patients.

Finally the clinical relationships of neocortical Lewy body pathology were analysed and compared with the group with brainstem and limbic Lewy body disease only.

Pathological methods

Pathological material was prepared using methods described earlier (Colosimo *et al.*, 2003). The definition of the neuropathological diagnosis of Parkinson's disease was depletion of neurons in the substantia nigra pars compacta associated with Lewy bodies in surviving nigral neurones in the context of a compatible clinical picture (Gibb and Lees, 1988b). Ninety brains that had been collected by the QSBB between 2001 and 2006 were examined using α -synuclein immunohistochemistry. All references to quantitative assessment of Lewy body and other pathologies refer to these cases. As part of an ongoing investigation the principles of the Consensus Guidelines for Pathological Diagnosis of Dementia with Lewy Bodies (McKeith *et al.*, 1996) were applied to all Parkinson's disease cases submitted to the QSBB in order to document the distribution and severity of Lewy body pathology. Sections of 7 μ m thickness from the following brain regions were examined: brainstem, including substantia nigra, transentorhinal cortex, cingulate cortex and three neocortical areas

(anterior frontal lobe with the second frontal gyrus, temporal cortex with the second temporal gyrus, and parietal cortex with inferior parietal cortex). These were stained with a polyclonal anti- α -synuclein antibody (Novocastra, UK) and assessed semi-quantitatively to derive a Lewy body score for each cortical area, summated to give a final score. In keeping with the Consensus Guidelines 1996 total scores of 7–10 were classified as neocortical Lewy body disease, 3–6 as transitional or limbic Lewy body disease while a score of 0–2 corresponded to brainstem Lewy body disease. The extent of any associated neurofibrillary tangle pathology was characterized by the approach described by Braak *et al.* (1991). To document Alzheimer plaque pathology, amyloid-A β immunohistochemistry (Dako, UK) or Bielschowsky's silver impregnation and CERAD (Consortium to Establish a Registry for Alzheimer's disease) criteria (Mirra *et al.*, 1991) were employed. A four-point, semiquantitative grading system was used for neocortical plaque pathology as follows: Grade 0, absent; Grade 1, sparse or occasional plaque pathology; Grade 2, moderate plaque pathology; and Grade 3, severe or plentiful plaque pathology. A β immunohistochemistry was also used to document cerebral amyloid angiopathy, the severity of which was compared across the subtypes (Revesz *et al.*, 2003).

Statistical methods

Group comparisons were made using χ^2 for categorical and two-tailed *t*-test or the Mann–Whitney U-test, as appropriate, for continuous variables, using STATISTICA version 6.0.

Results

Two hundred and forty-two cases of pathologically proven Parkinson's disease were studied (163 male, 79 female). Mean disease onset age was 61.0 years (range 29–85 years). Mean age at death was 76.3 years (range 52–94 years) and mean disease duration was 15.6 (range 3–41 years).

Subtype by clinical features at diagnosis

Sixty-one patients (25%) were classified as EDO, 88 (36%) as TD and 93 (38%) as NTD. Comparisons of clinical features are shown in Table 1. The EDO group (mean age at onset 47 years) had the longest disease duration (mean 22.5 years). In this group the motor phenotype before treatment was predominantly non-tremulous. Only 15 (23%) had tremor dominance and only one patient had midline motor deficits at diagnosis. Throughout the disease the EDO group had more motor fluctuations and received higher levodopa dosages than other subtypes. They also had the longest delay before the development of hallucinations, dementia, falling and need for residential care. Over the first decade of the disease course, this group developed less motor disability than the two older onset groups. The mean age at death of EDO cases (70.3 years) was significantly younger than the other two groups ($P < 0.05$). Frequent falling began 8 years prior to death in EDO, whereas it preceded death by about 5 years when it occurred in TD and NTD patients. When EDO patients developed dementia, death followed roughly 6 years later, compared with 4 years in TD and NTD patients.

Table 1 Clinical data for the three-subtype classification based on early clinical features (EDO, TD, NTD)

	EDO <i>n</i> = 61	TD <i>n</i> = 88	NTD <i>n</i> = 93	P-value EDO-TD	P-value EDO-TD	P-value TD-NTD
Age of onset	47.3 ± 6.5 (29–55)	66.1 ± 6.7 (55–85)	64.8 ± 6.5 (55–78)	<0.001	<0.001	NS
Disease duration (years)	22.5 ± 7.6 (3–34)	13.5 ± 4.7 (5–23)	12.9 ± 4.9 (3–22)	<0.001	<0.001	NS
Age at death	70.3 ± 6.9 (52–81)	79.5 ± 5.9 (65–94)	77.2 ± 9.37 (61–90)	0.03	0.04	NS
Tremor severity at diagnosis	0.8 ± 0.5	1.3 ± 0.5	0.6 ± 0.6	<0.001	0.03	<0.001
Time before levodopa (years)	3.3 ± 2.2 (0.5–10)	2.3 ± 1.7 (0.4–7)	1.4 ± 1.1 (0.1–6)	0.003	<0.001	<0.001
H&Y at 5 years	2.0 ± 0.3; <i>n</i> = 56	2.2 ± 0.5; <i>n</i> = 82	2.4 ± 0.6; <i>n</i> = 85	0.02	<0.001	0.08
H&Y at 8 years	2.2 ± 0.4; <i>n</i> = 52	2.4 ± 0.5; <i>n</i> = 69	2.8 ± 0.8; <i>n</i> = 77	0.02	<0.001	0.007
H&Y at 10 years	2.5 ± 0.6; <i>n</i> = 56	2.8 ± 0.6; <i>n</i> = 62	3.0 ± 0.7; <i>n</i> = 59	0.016	<0.001	NS
H&Y at 15 years	3.0 ± 0.7; <i>n</i> = 49	3.2 ± 0.7; <i>n</i> = 35	3.4 ± 0.8; <i>n</i> = 33	NS	0.01	NS
Levodopa dose at 5 years (mg)	696 ± 352 (0–2000)	5 ± 179 (0–1000)	636 ± 260 (0–1300)	0.001	NS	0.001
Levodopa dose at 10 years (mg)	804 ± 380 (0–2000)	672 ± 248 (0–1500)	5 ± 441 (450–2000)	NS	NS	0.002
Maximum severity motor fluctuations	2.12 ± 0.92 (0–3)	0.84 ± 0.98 (0–3)	1.55 ± 1.15 (0–3)	<0.001	0.047	0.013
Dyskinesia onset (years)	5.68 ± 4.6 (1–20)	9.0 ± 4.7 (6–20)	7.0 ± 2.6 (1–11)	0.02	NS	NS
Dementia onset (years)	16.2 ± 5.6 (10–27)	10.0 ± 4.3 (4–15)	8.7 ± 3.9 (3–11)	<0.001	<0.001	NS
Falls onset (years)	14.5 ± 6.8; <i>n</i> = 30	8.63 ± 4.18; <i>n</i> = 39	8.00 ± 4.65; <i>n</i> = 53	0.005	0.02	NS
Hallucinations onset (years)	17.1 ± 8.15; <i>n</i> = 33	9.22 ± 4.8; <i>n</i> = 42	8.38 ± 5.07; <i>n</i> = 46	0.002	0.016	NS
Age at fall onset (years)	62.5 ± 8.03; <i>n</i> = 33	74.1 ± 6.6; <i>n</i> = 42	72.6 ± 6.0; <i>n</i> = 46	<0.001	<0.001	NS

Results are shown as mean ± standard deviation (SD) (range).
NS = not significant.

The mean age of onset in the TD group was 66.1 years. This group had the least motor fluctuations and the lowest mean levodopa dosage (672 mg/day, range 0–1500 mg/day). Despite lower H&Y scores in the first 5–8 years, the mean disease duration of these patients (13.5 years) was not significantly longer than NTD (12.9 years, *t*-test: $P > 0.05$).

The mean age of onset in the NTD group was 64.8 years, which was not significantly different from the TD group. Dementia was significantly more common in the NTD group (57/93, 61%) compared with EDO (10/61, 16%, χ^2 : $P < 0.01$) and TD (28/88, 32%, χ^2 : $P < 0.05$). NTD patients had the highest degree of disability (H&Y grade) at 5 and 8 years, although the mean time to markers of advanced disease (frequent falling and residential care) was similar to the TD onset group.

On genetic screening, three cases were LRRK2 positive with Gly2019Ser mutations. Two belonged to the NTD phenotype and one to EDO.

The NTD group ($n = 35$) had a significantly higher mean Lewy body score (8.1 ± 2.0) than both EDO ($n = 26$; 6.5 ± 2.0 , Mann–Whitney U: $P = 0.003$) and TD ($n = 29$; 6.6 ± 2.0 ; Mann–Whitney U: $P = 0.003$) (Fig. 1). NTD cases had particularly heavy burdens of cortical Lewy bodies in the frontal regions (69% had Grade 2 and 22% Grade 1), more than EDO (40% Grade 2 and 21% Grade 1, χ^2 : $P = 0.002$), and TD (21% Grade 2 and 53% Grade 1, χ^2 : $P = 0.002$). Similarly, a transentorhinal Grade 2 Lewy body score was present in 88% of NTD cases, against 52% of EDO and 22% of TD (χ^2 : $P < 0.001$). Alzheimer disease neurofibrillary pathology was also significantly more prevalent in the NTD group (47%) than the EDO (16%, χ^2 : $P < 0.001$) or TD onset (19%, χ^2 : $P < 0.001$) groups, but, when present; this was mostly mild (Braak and Braak Stage I–II) type. Severe, high grade (Braak & Braak Stage V–VI) neurofibrillary changes were present in only two cases, who were both demented (one TD, one NTD). There was also a significant increase in severity of plaque formation in

the neocortex in NTD group (only 48% had zero plaque score compared 86% in to the EDO group and 72% in the TD, χ^2 : $P = 0.004$). Amyloid angiopathy was reported more frequently ($P = 0.047$) in NTD (22%), compared with 8% in TD and 6% in EDO.

Rapid disease progression without dementia

Patients who conformed to the RDP definition were selected out of the other subgroups, yielding the four-group analysis (Table 2). Of 20 cases identified with RDP characteristics, the majority (14/20) came from the TD group, and only one had earlier disease onset (Fig. 2A). Mean age of onset in the RDP group was 67.4 (range 43–80), similar to TD and NTD. The RDP patients were more likely to have had depression at Parkinson's disease onset (8/20, 40%) compared with EDO (11/55, 20%), TD (12/74, 15%) and NTD (19/79, 24%) patients. There were 14 cases in which the medical record review was inconclusive on the question of depression at the disease onset. The estimated depression scores within two years of diagnosis were significantly higher in the RDP group compared with EDO, TD (Mann–Whitney U: $P < 0.01$) and NTD ($P = 0.02$). Proportionately more RDP patients had early midline motor deficits (4/18, 22%) in comparison to TD (3/68, 4%) and EDO (1/57, 2%), although the ratio was similar for NTD (18/83, 21%). H&Y scale estimates reflect significantly faster accumulation of motor disability in the RDP group. The average age for onset of regular falls was close to the mean age of death for RDP, whereas this preceded death by about 5 years in TD and NTD, and by 8 years in EDO. The RDP patients also had the highest mean levodopa dosage at 5 years. Patients who clearly died prematurely of an unrelated disease had been excluded from the RDP group; most patients died from the effects of severe

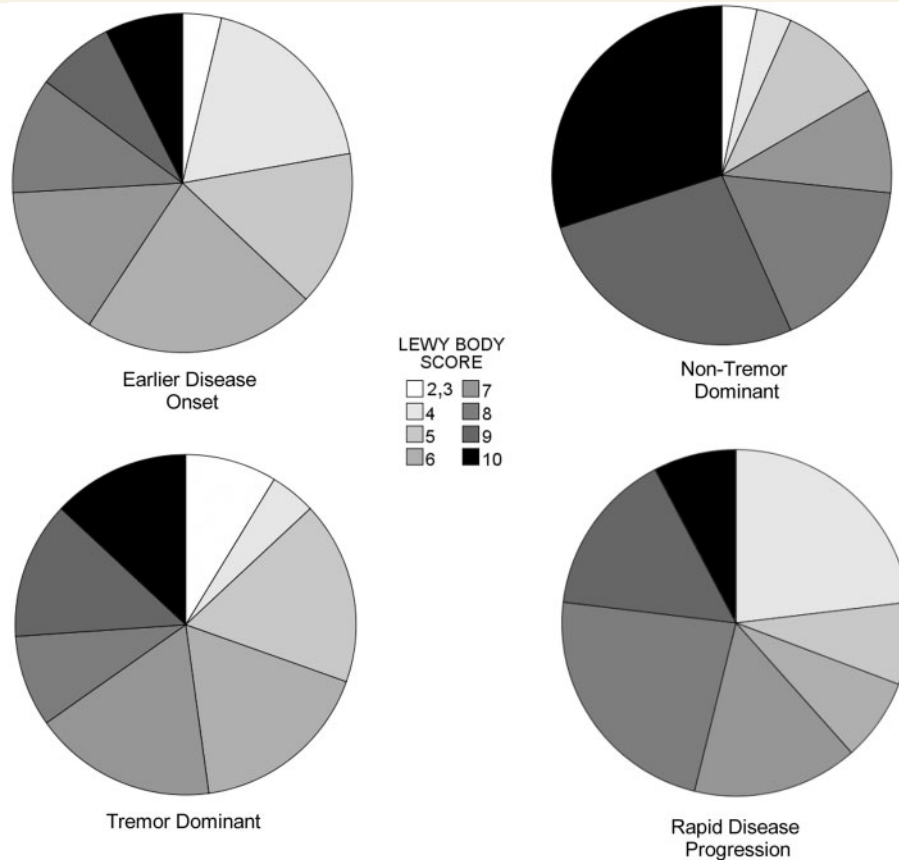


Figure 1 Lewy body scores according to clinical subtypes.

Table 2 Clinical data in the four-subtype classification of Parkinson's disease

	EDO n = 60	TD n = 74	NTD n = 88	RDP n = 20	P-value EDO-RDP	P-value TD-NTD	P-value TD-RDP	P-value NTD-RDP
Age of onset	47.4 ± 6.6 (29–55)	65.6 ± 6.8 (55–85)	64.6 ± 6.6 (55–78)	67.4 ± 7.9 (43–80)	<0.001	NS	NS	NS
Age of death	70.6 ± 6.6 (54.5–81)	80.0 ± 5.9 (72–94)	78.0 ± 5.8 (61–93)	75.1 ± 7.6 (52–88)	0.01	0.034	0.002	NS
Bradykinesia severity at diagnosis	0.9 ± 0.7	0.5 ± 0.5	1.3 ± 0.5	1.4 ± 0.7	0.04	<0.001	<0.001	NS
Tremor severity at diagnosis	0.8 ± 0.5	1.3 ± 0.4	0.5 ± 0.5	1.3 ± 0.8	0.009	<0.001	NS	<0.001
Time before levodopa, year	3.3 ± 2.2 (0.5–10)	2.4 ± 1.7 (1–8)	1.43 ± 1.1 (0.1–6)	1.4 ± 1.2 (0.4–3)	<0.001	0.001	0.012	NS
Levodopa dose at 5 years (mg)	683 ± 350 (0–2000)	491 ± 144 (0–1000)	425 ± 147 (0–1300)	2 ± 193 (180–1000)	NS	0.002	<0.001	0.004
Dyskinesia severity at 5 years	0.9 ± 0.9	0.3 ± 0.5	0.4 ± 0.8	1.1 ± 0.9	NS	0.011	<0.001	NS
H&Y at 5 years	2.0 ± 0.3	2.1 ± 0.4	2.4 ± 0.6	3.0 ± 0.4	<0.001	0.002	<0.001	<0.001
H&Y at 8 years	2.2 ± 0.4	2.4 ± 0.5	2.8 ± 0.8	3.6 ± 0.5	<0.001	0.002	<0.001	<0.001
Depression score in 2–3 years of diagnosis	1.6 ± 0.8; n = 46	1.5 ± 0.7; n = 50	1.9 ± 0.8; n = 51	2.6 ± 0.5; n = 8	0.0013	0.02	<0.001	0.02
Falls onset (years)	14.8 ± 6.9; n = 31	9.4 ± 4.0; n = 32	8.3 ± 4.5; n = 50	5.9 ± 2.1; n = 8	<0.001	NS	0.027	NS
Hallucinations onset, (years)	17.7 ± 7.6; n = 33	9.8 ± 4.7; n = 36	8.73 ± 4.9; n = 43	6.5 ± 2.4; n = 8	<0.001	NS	NS	NS
Age at fall onset (years)	62.5 ± 8.0; n = 32	74.5 ± 5.7; n = 35	72.5 ± 6.1; n = 46	71.5 ± 8.6; n = 10	0.001	NS	NS	NS

Results are shown as mean ± SD (range).
NS = not significant.

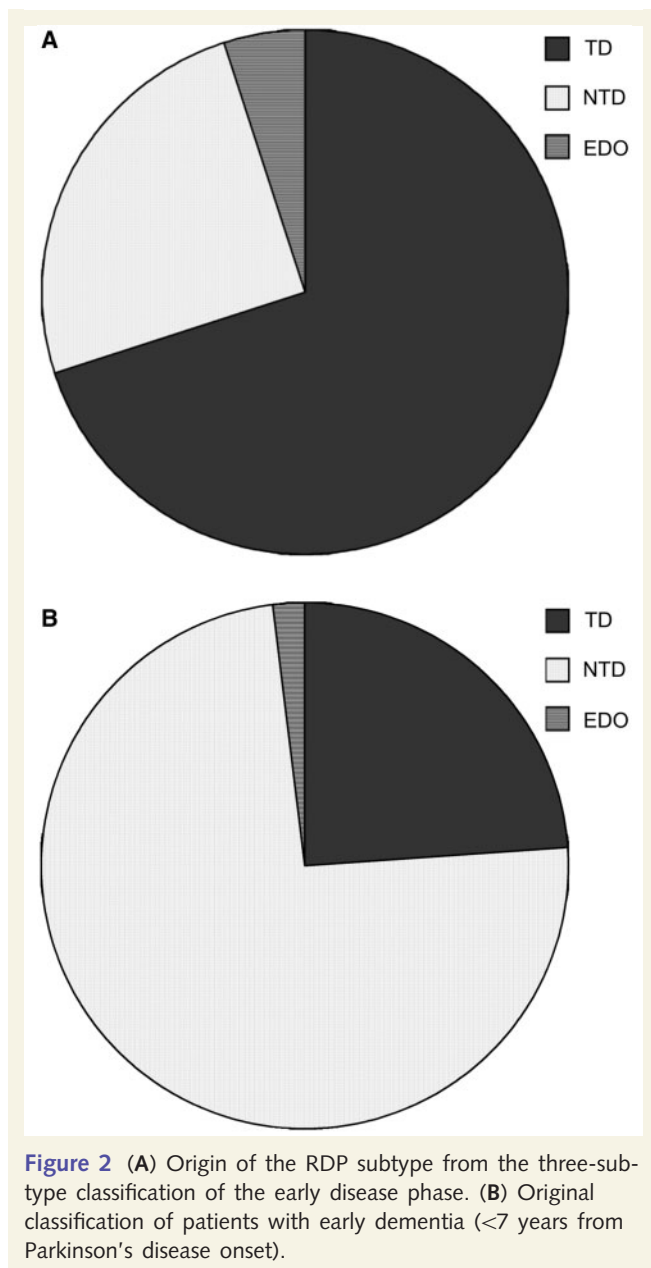


Figure 2 (A) Origin of the RDP subtype from the three-subtype classification of the early disease phase. (B) Original classification of patients with early dementia (<7 years from Parkinson's disease onset).

motor disability, or from an intercurrent medical disorder when already severely disabled. This group had a significantly lower mean Lewy body score (6.7 ± 1.6 , $n=8$) than NTD (8.1 ± 2.1 , $n=32$, Mann–Whitney U: $P=0.03$), but there was little difference when compared with EDO (6.6 ± 2.0 , $n=25$, Mann–Whitney U: $P>0.05$) and TD (6.5 ± 2.2 , $n=25$, Mann–Whitney U: $P>0.05$) (Fig. 1).

Young onset Parkinson's disease (age 21–40 years)

Thirteen patients (5.4% of the entire sample) conformed to this definition. Mean age of onset was 35.9 ± 3.6 (range 29–40), and mean disease duration was 31.1 ± 4.6 (range 26–40) years,

significantly longer than for patients with age at onset 41–54 years (20.8 years, t -test: $P<0.0001$). However, these two age at onset groups were not significantly different for any of the following clinical comparisons: H&Y score over first 8 years, time to initiation of levodopa therapy, time to onset of falling. All Young Onset (21–40 years) cases were documented to have a fluctuating response to levodopa treatment. Six eventually developed visual hallucinations, and two were demented by the time of death. Lewy body scoring was only available on five Young Onset Parkinson's disease cases; mean Lewy body score was 6.4, which was little different to the mean score of 6.6 in patients who had developed Parkinson's disease between 41 and 54 years of age.

Dementia

Out of 242 patients, 105 (43%) developed Parkinson's disease-dementia. The mean disease duration to death was 13.8 ± 5.7 years for those with dementia and 17.0 ± 7.6 years for those without. (t -test: $P<0.001$). Mean age at Parkinson's disease onset for demented patients was 62.5 ± 9.4 and 59.2 ± 10.4 for non-demented (t -test: $P=0.004$). Lewy body score was 7.6 ± 2.1 for those with dementia and 6.5 ± 2.1 for those without (Mann–Whitney U: $P=0.011$).

Early dementia

Forty-six patients had developed dementia within the first 7 years of disease. Patients with the NTD subtype (74%) were significantly over-represented in this group (χ^2 : $P<0.001$) in the NTD group when compared with TD (24%) and EDO (2%) (Fig. 2B). The mean age at onset of those with early dementia was 68.4 ± 8.0 years and their mean disease duration was 9.2 ± 2.9 years. Thirteen (6% of the entire sample) became demented before the age of 65 years. Of these, only one had TD onset, compared with 12 with NTD onset. All four patients with dementia diagnosed before the age of 55 years had the NTD phenotype. Depression was present at the time of diagnosis in 23% of patients with early dementia, which was no different to the percentage in all other cases.

The group with early dementia had a mean total Lewy body score of 8.2 ± 2.4 . Compared with the four subtype classification of patients who did not dement early, the early dementia cases had significantly greater mean Lewy body scores than EDO (6.5 ± 1.9 , Mann–Whitney U: $P=0.014$), TD (6.4 ± 1.8 , Mann–Whitney U: $P=0.014$), but not significantly more than the RDP (6.8 ± 2.4 , Mann–Whitney U: $P=0.16$) and the NTD (7.8 ± 2.1 Mann–Whitney U: $P=0.66$) groups. There was no significant difference in heavy deposition (Grade 2) of frontal cortical Lewy bodies between NTD patients with early dementia (75%) and NTD patients without early dementia (71%). Alzheimer pathology was significantly more prevalent in the early dementia group. It was present in 71%, though it was of low grade (Braak & Braak Stages I–II) in more than half; 21% had Braak & Braak Stage III–IV pathology and two cases (14%) had Braak & Braak Stage V–VI. Neocortical A β plaques were more common in patients with early dementia than all others. Median plaque grade was 2 for early dementia, 1 for NTD without early dementia and 0 for EDO and TD without early dementia, and for RDP (χ^2 : $P<0.001$ for all

comparisons). Amyloid angiopathy was more common in patients with early dementia (33%) than in EDO (6%), TD (5%), NTD (21%) cases who did not dementia early and in RDP (7%) (χ^2 : $P=0.01$).

Early midline motor involvement

Twenty-six patients had axial motor signs or symptoms that were documented at the time of diagnosis. Compared with the other cases, early midline motor involvement was associated with a significantly older mean age of onset (67.5 ± 6.4 years, t -test: $P=0.045$), and shorter disease duration (10.4 ± 4.0 years, t -test: $P=0.009$). These patients also had less motor fluctuation (0.5 ± 0.7 versus others 1.6 ± 1.1 , Mann–Whitney U: $P=0.013$), earlier falling (7.8 ± 4.5 years versus others 11.6 ± 5.2 years, Mann–Whitney U: $P=0.012$), earlier development of cognitive disability (7.1 ± 4.2 years versus others 13.7 ± 6.5 years, Mann–Whitney U: $P=0.009$) and earlier requirement for residential care (6.8 ± 4.1 years versus others 12.3 ± 6.2 years, Mann–Whitney U: $P=0.007$). In 16 cases, the presence or absence of early midline motor deficits could not reliably be determined from the medical records. In the four-subgroup classification, most patients with early midline motor involvement had NTD features (19 patients), then RDP (four patients), TD (three patients), with only one patient from the EDO group. The mean cortical Lewy body score was not significantly different between early midline motor involvement cases (7.8 ± 2.04) and others (7.1 ± 2.1).

Neocortical Lewy body disease

To examine the extent to which pathology predicts clinical features, we compared pathological grades with clinical groups. We dichotomized patients according to the extent of Lewy body pathology as follows: brainstem/limbic disease (Lewy body score 1–7); and neocortical disease (Lewy body score >7). There was a significant difference in the subtype make-up of these two classes. Patients with brainstem/limbic Lewy body scores were more likely to be EDO or TD and those with neocortical Lewy body disease were more likely to be NTD (χ^2 : $P=0.002$), while RDP was

approximately equally represented in each (Fig. 3). There were, however, no significant differences between Lewy body classes for age of Parkinson's disease onset (58.7 ± 10.3 and 62.3 ± 9.5 years), for age at death (75.0 ± 7.8 and 77.4 ± 8.1 years), for disease duration (16.5 ± 7.6 and 15.4 ± 6.5 years) and for time to onset of dementia (12.6 ± 6.1 and 11.7 ± 4.6 years). Neocortical Lewy body disease was significantly more commonly present in demented cases (χ^2 : $P=0.0005$). The neocortical Lewy body class was associated with more severe bradykinesia (Mann–Whitney U: $P=0.04$), more frequent midline symptoms at onset (Mann–Whitney U: $P=0.012$) and more falls (Mann–Whitney U: $P=0.04$) than localized/limbic Lewy body disease. Mean time to onset of hallucinations was longer in the localized/limbic Lewy body class (15.3 ± 8.6 years) compared with those with neocortical Lewy body disease (10.6 ± 6.0 years, t -test: $P=0.024$).

Discussion

This retrospective study of clinical subgroups in Parkinson's disease has identified some clinical and pathological correlations with patterns of disease onset and progression. A classification system based on a previous cluster analysis performed without *a priori* assumptions was used as the starting point for this clinicopathological analysis. We found that patients with NTD onset had more severe cortical Lewy body pathology and were more likely to suffer from dementia than those in other clinical groups. In contrast to previous studies, we found no significant difference in disease duration between patients with TD and NTD onset, although the TD onset group had less H&Y stage progression over the first 8 years of the disease course. A smaller subgroup of patients with rapid disease progression but without dementia was identifiable, and a substantial proportion of this group was derived from the tremor group, further challenging the traditional concept of a benign course for tremulous Parkinson's disease.

To determine the subtype definitions for our analysis, we reviewed the two surveys of Parkinson's disease that had used cluster analysis methodology without prospective assumptions

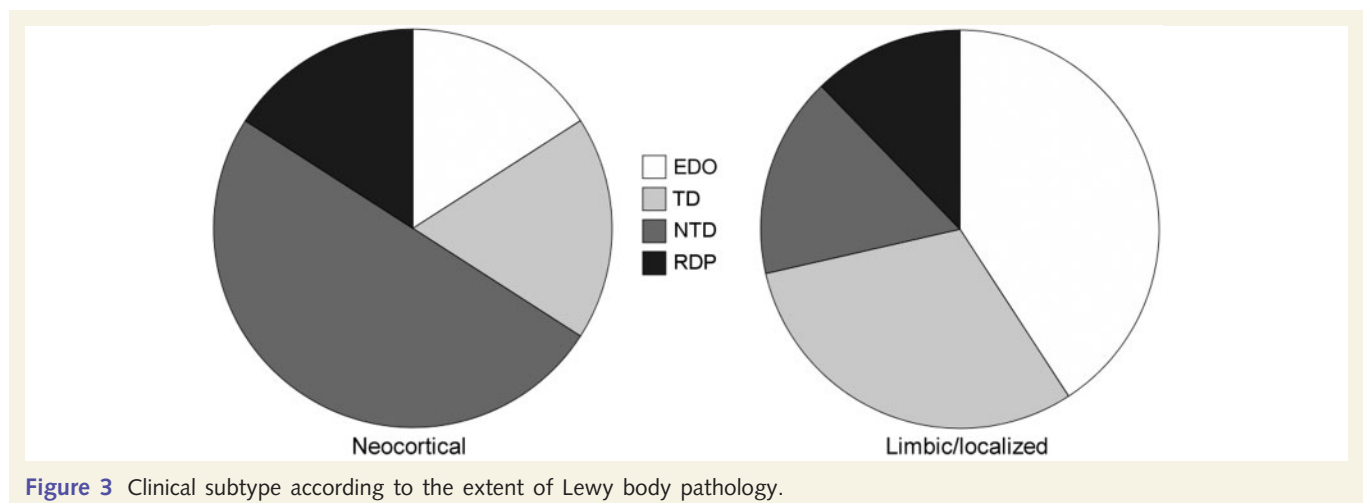


Figure 3 Clinical subtype according to the extent of Lewy body pathology.

about categorization. The study of Graham and Sagar segregated their Parkinson's disease sample into five subgroups, but two of these groups had long mean disease durations and were thought to be later stage examples of their other subgroups. They concluded that there are three basic groupings: 'motor only', with well preserved cognitive function, 'motor and cognitive', and 'rapid progression', containing older onset cases with rapid progression of both motor and cognitive disability (Graham and Sagar, 1999). All clinical data were used in their cluster analysis. The mean disease duration in the Lewis *et al.* (2005) study was 7.8 years, similar to that of Graham and Sagar, although they restricted their sample to H&Y Stages I–III and claimed, by virtue of excluding cases with advanced disease, to have a more representative sample of mild to moderate Parkinson's disease. Their methodology did not use all the clinical data in the cluster analysis, reserving some disease characteristics for *post hoc* comparisons. They presented three-, four- and five-group clustering solutions. The three basic groups were younger disease onset, tremor dominant and non-tremor dominant with cognitive decline. In the four-group system, a rapidly progressive subtype without dementia emerged. Five groupings only served to divide non-tremor dominance into cases with moderate and severe cognitive deficits. There are broad similarities between these two classification systems, but we chose the Lewis *et al.* (2005) scheme because its groupings were better delineated, and were able to be simply defined. We also concentrated on pre-treatment medical records to define tremor- and non-tremor dominance. One weakness of the two data-driven studies is their reliance on motor scoring on optimum drug treatment, which may have obscured pre-treatment patterns of motor deficit.

The Lewis subtypes represent clusters of clinical features, so definitions had to be improvised in order to classify the Brain Bank cases. The decision to take 55 years as the age cut-off for disease onset on the EDO group was guided by the mean age of 50 years in this group in the Lewis *et al.* study, and resulted in a slightly earlier mean age of onset in our EDO subdivision. By designing subtype definitions that matched only the core subtype attributes, other clinical and pathological characteristics were available to check the validity of the classifications. Our version of the NTD phenotype at presentation uncoupled the Lewis *et al.* linkage with cognitive decline. However, cognitive disability was then analysed across the subgroups, and an early dementia grouping was created to cross-check the correlations of cognitive decline. Our definition of RDP without dementia relied on identifying cases with a short disease course, preserved cognition and exclusion of premature death from other causes.

The findings do not support the notion of tremor as an independent indicator of a longer and more slowly progressive disease course. The mean disease duration of the TD clinical subtype was only 7 months longer than NTD onset cases. Reclassification of the RDP cases in the four-subtype analysis extended the difference in mean disease duration between TD and NTD groups to a little over 1 year. In the clinic, so-called benign tremulous Parkinson's disease is encountered from time to time. Josephs *et al.* (2006) found that 14% of tremor dominant patients fitted a benign tremulous definition of little progression of non-tremor motor deficits after 8 years. All benign tremulous cases

in that study had rest tremor which was relatively unresponsive to levodopa, and many had a family history of tremor. Clarimón *et al.* (2008) identified similar clinical characteristics in a longitudinal study of 26 cases who had mixed rest and postural tremor, and little bradykinesia or rigidity. Having followed the broad TD subtype definition set by Lewis, we could not focus on benign tremulous Parkinson's disease patients in the current study but we found little evidence of a positive effect on prognosis based on tremor as the dominant symptom at presentation. Further direct study on tremulous Parkinson's disease is required to understand the origin of the benign course in some patients. Imaging studies show that rest tremor is usually associated with a dopaminergic deficit (Brooks *et al.*, 1992). However, some cases that conform to the benign tremulous Parkinson's disease phenotype in life do not have the pathology of Parkinson's disease (Rajput *et al.*, 2008) and may represent examples of dystonic tremor (Schneider *et al.*, 2007).

Our results confirm the Lewis subgrouping conjunction of a non-tremor motor deficit with cognitive decline. Our NTD group was identified from the clinical features at diagnosis, but significantly more patients developed dementia, and the mean burden of cortical Lewy body disease was significantly greater than in the other groups. Early cognitive disability within 7 years of onset was also strongly associated with a NTD phenotype, and these early dementia patients had similar cortical Lewy body scores to NTD cases. A postural instability/gait difficulty phenotype can be equated with early midline motor involvement, and this feature was also associated with early cognitive decline. However, the NTD classification alone was the strongest predictor of high mean cortical Lewy body score. The overall prevalence of dementia was, at 43%, relatively lower than found in some prospective clinical surveys of cognition in Parkinson's disease (Buter *et al.*, 2008; Hely *et al.*, 2008). Retrospective studies of dementia are prone to under-ascertainment. Cases of dementia would not have been documented by treating neurologists or gerontologists until a certain level of disability had been reached, and lesser degrees of cognitive impairment may not have been documented at all. Another source of reduced accuracy was the determination of onset of dementia from records made at regular outpatient clinic visits, which may have tended to post-date the start of a cognitive deficit. The exclusion of cases of established dementia within 2 years of onset of Parkinson's disease allowed for the reduced sensitivity to the onset of cognitive impairment, and ensured that all demented cases could be classified as Parkinson's disease-dementia.

The EDO group analysis confirmed previous reports that these patients have significantly longer disease duration, slower progression of motor disability and more motor fluctuations and dyskinesia than other groups (Parkinson Study Group, 1996; Schrag and Quinn, 2000). The majority had non-tremor dominant motor deficits at diagnosis. Lewis *et al.* (2005) and other clinical studies have identified preservation of cognitive function as a defining feature of the EDO subtype. Dementia was uncommon before the age of 65 years in our study, so there were relatively few EDO patients who developed dementia over the first 10–15 years of the disease. But, when the entire disease course is taken into account, cognitive decline and dementia eventually affected a

substantial number of EDO cases. The amount of cortical Lewy body pathology was no less than the older onset TD and RDP subgroups. The number of patients with conventionally defined 'young onset Parkinson's disease' commencing between 21 and 40 years of age (Quinn *et al.*, 1987, Schrag *et al.*, 1998) was small. Their disease course was significantly longer than the remainder of our EDO group, yet they resembled it in most other ways. Visual hallucinations, cognitive decline and heavy cortical Lewy body deposition did occur in some of these cases.

Rapid disease progression without dementia would be the least recognized of Lewis subgroups by clinicians. Their cluster analysis produced a RDP group which contained 17% of their total sample. In our four-subtype analysis, using a definition which approximates the Lewis grouping, only 8% of QSBB cases had this phenotype. Although smaller, our group matched the Lewis subtypes in several ways. The majority of the patients with RDP of each study were drawn from the TD group in the three group classification. RDP was closely linked to an older than average age of presentation, with only one case re-classified from EDO type. Another point of agreement was early depression, which, in both studies, was associated with RDP more strongly than the other groups. Our RDP group had the highest mean levodopa dosage, whereas corresponding patients in the Lewis study were taking relatively small doses. This difference might be explained by the fact that we surveyed the entire disease course and not just its first part. Our definition of RDP minimized the possibility that the grouping contained an excess of patients who died prematurely of unrelated medical disorders. The RDP clinical pattern is not clearly identified in any other subtyping scheme. Graham and Sagar identified a relatively old and rapidly progressive subgroup, but did not discriminate cognitive preservation from cognitive decline. With a relatively small proportion of RDP patients and with no distinguishing pathological findings, the obscurity of this subgroup in the clinical practice it is not surprising. The rapid progression of motor disability could be confused with progressive supranuclear palsy-Parkinsonism or multiple system atrophy-Parkinsonism (Quinn, 2005; Williams *et al.*, 2005). But it may be possible to recognize such cases in life where older age of onset, early depression and quickly increasing motor disability with early midline involvement coexist.

We were able to analyse these relationships by further working backwards from the pathological features. Although it is recognized that the pathology represents the end stage of disease, and may not be representative of the dynamic processes that evolve during decades of illness, it is instructive that the end-stage Lewy body pathology itself does appear to predict certain clinical characteristics. Most striking were the findings that patients with neocortical Lewy body disease were much more likely to have a NTD phenotype, and those with brainstem/limbic pathology were more likely to have EDO or TD phenotypes. In our study, the main clinical correlations of Lewy body scores were bradykinetic onset and cognitive dysfunction. The higher cortical Lewy body scores in the NTD patients compared with TD and RDP were not explained by effects of age, as age at death was not significantly different between these groups. These findings should be considered in the context of the recent examination of 87 brains with Lewy body pathology, where Halliday *et al.* (2008) identified three

clinico-pathological groupings: (i) patients with younger onset and long duration disease, where the distribution of Lewy bodies best fits the Braak staging scheme (Braak *et al.*, 2003); (ii) a dementia dominant syndrome, with severe neocortical Lewy body changes from the outset of clinical disease; and (iii) an older onset group that had a shorter mean disease course, more cognitive decline, higher Lewy body loads and a higher proportion of other neuropathologies (Halliday *et al.*, 2008). These patients were analysed with respect to disease duration to explore patterns of evolution of pathology, and Group 2 contained cases of dementia with Lewy bodies that may have been excluded by our entry criteria. The other two groups do not neatly fit into our classifications, but there were some similarities. The Halliday Group 1 is similar to our EDO group, where we found a range of Lewy body pathology. Heavy burdens of Lewy body and non-Lewy body pathology were not present in our RDP subgroup, in which the other attributes of Halliday *et al.* (2008) group 3 (older onset and rapid motor progression) were separated from cognitive dysfunction. In our clinico-pathological survey, cognitive impairment was associated with greater amounts of neocortical amyloid plaque and Alzheimer neurofibrillary pathology, although the latter was relatively mild in most cases. However, a significant association between cortical parenchymal A β plaque load and Lewy body burden has been shown by several studies, indicating that A β deposition may be an important factor contributing to the aggregation cascade of α -synuclein in Lewy body disorders (Pletnikova *et al.*, 2005; Lashley *et al.*, 2008). Lewy body deposition appeared to be the dominant cortical pathology in our RDP group.

In our study, the natural history and the pathological findings represent the most robust data. Clinical details were gathered from medical records that had been collected by many different physicians, and retrospective information of this sort has inherent weaknesses. Initial, pre-treatment symptoms and patterns of extrapyramidal signs were usually recorded clearly. Thereafter, clinical records documented treatment details, and contained problem-orientated information concerning motor fluctuations, dyskinesia, and other aspects of disease progression, such as falling, hallucinations and cognitive deficits. The QSBB case files contained insufficient numerical data on motor and cognitive function for the type of cluster analysis performed by Lewis *et al.* (2005) and Graham and Sagar (1999), but its clinical and pathological information could be cross-referenced with the subtype classifications.

Although the cluster analysis methodology of Lewis *et al.* (2005) provides a useful framework for a clinico-pathological subtype study, and although the QSBB data gives considerable support to their scheme, theirs is not the only way to sub-classify Parkinson's disease. Further data-driven clinical research with longitudinal observation in large patient groups is needed to distinguish the variations of Parkinson's disease and to show how these variations relate to progression. The following conclusions about basic phenotypic features are drawn from our analysis, and are generally applicable to subtyping systems:

- The association between bradykinetic onset, dementia and high Lewy body burden is strong, and is likely to have a biological basis.

- Among patients with tremor predominant onset, there may be a smaller group that fits a benign tremulous pattern, as defined by Joseph *et al.* (2006). However, tremor alone does not predict a significantly longer survival.
- The identification of early midline motor disability was equated with the previously described postural instability/gait difficulty subtype. This characteristic was not more predictive than bradykinetic onset for dementia and high Lewy body score.
- Early onset Parkinson's disease was shown to have many of the features usually attributed to it—long disease course, relatively slow progression, and more motor fluctuations and dyskinesia. However, as these patients age, they lose some of this clinical distinctiveness and may develop features of advanced Parkinson's disease including cognitive disability. Pathologically, they have no less Lewy body burden than older onset groups without bradykinetic dominance.

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