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Relationships between age and late progression of Parkinson's disease: a clinico-pathological study

Peter A. Kempster,[1,2,3] Sean S. O'Sullivan,[1,2] Janice L. Holton,[1,2] Tamas Revesz[2] and Andrew J. Lees[1,2]

1 Reta Lila Weston Institute of Neurological Studies, UCL Institute of Neurology, University College London, London, WC1N 1PJ, UK
2 Queen Square Brain Bank for Neurological Disorders and UCL Institute of Neurology, University College London, London, WC1N 1PJ, UK
3 Neurosciences Department, Monash Medical Centre and Monash University, Clayton, 3168, Melbourne, Australia

Correspondence to: Professor A.J. Lees,
Reta Lila Weston Institute of Neurological Studies,
University College London,
1 Wakefield Street,
London WC1N 1PJ, UK
E-mail: alees@ion.ucl.ac.uk

To investigate the relationships between age, the advanced clinical stages of Parkinson's disease and neuropathology, we surveyed 129 case records from donors with pathologically proven Parkinson's disease at the Queen Square Brain Bank for Neurological Disorders. Cases were separated into five groups according to age at death, thus comparing patients who reached the advanced stage of the disease at different ages. Four milestones of advanced disease (frequent falls, visual hallucinations, dementia and need for residential care) occurred at a similar time from death in each group. There were no significant differences in disease duration across these age groupings, nor were there differences in the severity and distribution of Lewy body and other pathologies. The milestones of dementia ($P < 0.0005$) and visual hallucinations ($P = 0.02$) as well as the accumulation of multiple milestones ($P < 0.0005$) were associated with high cortical Lewy body scores. Demented cases also had significantly more Alzheimer neurofibrillary and amyloid-β plaque pathology. Correlation analysis showed that the time intervals between disease onset and recording of milestones were strongly influenced by age at onset ($P < 0.0001$) and by total disease duration ($P < 0.0001$). The advanced disease phase plays out in a similar fashion at whatever age it occurs, with a common pathological endpoint. The clinico-pathological comparisons for the final stage of Parkinson's disease do support a staging system based on the rostral extent and severity of Lewy body pathology, although other pathologies may play a synergistic role in causing cognitive disability. The chief effects of age on the rate of progression are seen over the early–middle part of the disease. An exponential curve for clinical progression provides the best explanation for these observations about age and the disease course.

Keywords: Parkinson's disease; dementia; visual hallucination; alpha-synuclein; Lewy body
Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease

Introduction

It is not now possible to study the clinico-pathological progression of Parkinson's disease without reference to the staging system of Braak and colleagues. By collating a series of meticulous cross-sectional observations on a collection of brains with incidental Lewy body pathology and clinically diagnosed Parkinson's disease, they derived a hierarchical, caudal to rostral six-stage scheme

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culminating in widespread neocortical Lewy body degeneration (Braak *et al.*, 2003*a*). The classification has simplicity and authority, and it resonates with clinical observations such as the recognition of prodromal hyposmia, autonomic symptoms and rapid eye movement sleep behaviour disorder in some patients. The suggestion of a prion-like mechanism of spread in Parkinson's disease that involves permissive templating would also fit with the Braak hypothesis (Braak *et al.*, 2003*b*; Brundin *et al.*, 2008; Olanow and Prusiner, 2009). Nevertheless, the scheme proposed by Braak remains unproven, and recent pathological research has highlighted some of its inconsistencies. A subgroup of brains from patients with typical Parkinson's disease transgresses the Braak staging rules (Kalaitzakis *et al.*, 2008). In one series containing cases not diagnosed in life with Parkinson's disease, almost half of those found to have alpha-synuclein pathology failed to display the typical caudorostral gradation (Zaccai *et al.*, 2008). In individuals without dementia or parkinsonism, the correlation between Braak stage and age is weaker than would be expected if the early stages always evolve to later stages (Burke *et al.*, 2008). Older patients who present with dementia rather than Parkinson's disease may have a limbic-predominant pattern of Lewy body deposition that initially bypasses the brainstem (Beach *et al.*, 2009). A study of mild cognitive impairment without parkinsonism suggested that a rostral to caudal pattern of Lewy pathology spread might best explain the pattern of neuropathology in some cases (Molano *et al.*, 2010). On the other hand, Markesbery *et al.* (2009) found that Lewy body deposition in cognitively intact elderly patients who did not have a movement disorder generally followed the Braak staging rules, and they concluded that these cases most likely represented the presymptomatic phase of Parkinson's disease or dementia with Lewy bodies. It has been suggested that variable protocols for processing, analysing and interpreting pathological material might be responsible for some discrepancies in estimating compliance with the Braak staging theory (Lim *et al.*, 2009), and a recent neuropathological consensus paper develops guidelines that could be helpful in standardizing future research (Dickson *et al.*, 2009).

Connecting the Braak observations with the Braak hypothesis are two postulates: (i) that the alpha-synucleinopathy of Parkinson's disease represents a pathological continuum and the laws which govern its progression can be determined; and (ii) that Lewy body deposition is not simply a consequence of ageing, but is integral to the pathological process underlying Parkinson's disease (Braak *et al.*, 2006). Together, these postulates refer to factors that are unique to a specific form of neuropathology, as opposed to factors that are common to ageing of the nervous system.

A previous clinico-pathological study of Queen Square Brain Bank for Neurological Disorders cases began as a search for the pathological correlates of different patterns of levodopa responsiveness (Kempster *et al.*, 2007). It revealed two main groups of patients: one with a younger onset and longer disease duration who had a strong but fluctuating response to levodopa, and another older onset group with a shorter disease course who did not fluctuate because, it was assumed, they had weaker levodopa responses. The mean age at death for these groups was almost the same, and there were no significant pathological differences using standard histopathological methods. In both groups, death was preceded by a similar advanced disease phase of increasing physical and cognitive disability. These findings suggested that ageing might accelerate progression after the age of 70 years, irrespective of previous disease duration or age of onset. However, the common age at death meant that patients who passed through the advanced disease state at different ages were not compared, and that disease-specific and age-related factors were hard to disentangle.

We have attempted to examine the effect of age on the clinico-pathological progression of Parkinson's disease by concentrating on the final phase of the clinical disease and the neuropathological changes that were present at its conclusion. Our aims were to differentiate processes intrinsic to Lewy body pathology from the influences of age, and to consider our findings in relation to current theories about the spread of alpha-synuclein and other pathologies. Clinically well documented Queen Square Brain Bank for Neurological Disorders cases with pathologically proven Parkinson's disease were separated into groups that reached the advanced disease stage at different ages, as defined by their age at death.

Material and methods

Patients with an initial diagnosis of parkinsonism and a pathologically proven diagnosis of Parkinson's disease established at autopsy between 2001 and 2008 were identified from the records of donors to the Queen Square Brain Bank for Neurological Disorders. Patients with a primary initial diagnosis of dementia were excluded. Eligible cases were selected by scrutiny of the clinical and pathological reports held on a database containing information on 430 brain donors. The London Multi-Centre Research Ethics Committee had approved procedures for the donation of brains to the Queen Square Brain Bank for Neurological Disorders as well as retention of and access to clinical records. Clinical and pathological data on 97 patients included in this study have been published before (Kempster *et al.*, 2007).

Medical record review

We performed a systematic review of the case files. All patients had been assessed by hospital specialists (neurologists or geriatricians with a specialist interest in Parkinson's disease). Cases were excluded if the medical records did not contain regular and well-documented reports of the disease course and pharmacological treatment. The onset of Parkinson's disease was defined by the time of firm diagnosis, not the retrospective report of first symptoms. The maximum levodopa dose and dopamine receptor agonist usage were noted.

The four milestones of disease advancement had been selected on the basis that each was likely to require additional medical attention and to be well recorded in the patient's dossier. The following definitions were used.

(i) Frequent falling: a notation in the clinical record, not necessarily quantified, that multiple falls were occurring. Isolated falls were ignored, even if fractures had resulted.
(ii) Visual hallucinations: reporting of persistent formed visual hallucinations; brief episodes of hallucination related to sepsis or alteration of medication were excluded.

(iii) Cognitive disability: substantial and persistent impairment of ability to perform tasks of daily living because of reduced cognitive function (Diagnostic and Statistical Manual of Mental Disorders-IV severity criterion for dementia).
(iv) Nursing home placement: long term admission to a residential high-level care facility.

The year of onset of each of these was recorded. The first recording of visual hallucinations or falling was taken as the time of onset. The fact that the symptoms often began some time before a clinic visit potentially reduced the accuracy of these determinations.

Pathological methods

Pathological material was prepared using methods previously described (Lashley *et al.*, 2008). The definition of the neuropathological diagnosis of Parkinson's disease was severe depletion of neurons in the substantia nigra pars compacta associated with Lewy bodies in surviving nigral neurons in the context of a compatible clinical picture (Gibb and Lees, 1988). The Consensus Guidelines for Pathological Diagnosis of Dementia with Lewy Bodies (McKeith *et al.*, 1996) were applied to all cases of Parkinson's disease submitted to the Queen Square Brain Bank for Neurological Disorders during and after 2001 in order to document the distribution and severity of Lewy body pathology. Seven-micron thick sections of brainstem (including the 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) were stained with a monoclonal anti-alpha-synuclein antibody (Novocastra, UK). Semi-quantitative assessments were used to derive a Lewy body score for each cortical area and summated to give a final score. In keeping with the Consensus Guidelines, total scores of 7–10 were classified as neocortical Lewy body disease, 3–6 as transitional or limbic Lewy body disease and 0–2 as brainstem Lewy body disease. The extent of any associated neurofibrillary tangle pathology was characterized by the six-stage classification described by Braak and Braak (Braak and Braak 1991). To document Alzheimer plaque pathology, amyloid-β immunohistochemistry (Dako, UK) and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria (Mirra and Braak 1991) were employed. A four-point, semi-quantitative grading system was applied 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 frequent plaque pathology.

Statistical methods

Group comparisons were made using χ^2 for categorical information and two-tailed *t*-test or the Mann–Whitney *U*-test, as appropriate, for continuous variables. For Lewy body scores, which were not normally distributed, Spearman's rho correlation was used. All other univariate correlations were calculated by Pearson's method. Cox multiple regression analyses were used to identify clinical factors that independently influenced milestone-free disease durations. These included gender as a categorical covariate, with age at death, total disease duration, total Lewy body score and neurofibrillary tangle stage as continuous variables. Statistical analyses of data were performed with Statistical Package for the Social Sciences version 14.0 (SPSS, Chicago, IL).

Results

Of 147 potential cases, 18 had been excluded because of insufficient clinical documentation. There remained 129 pathologically proven cases of Parkinson's disease (88 male and 41 female, mean age at diagnosis 61.9 ± 10.7 years).

The mean age at death for the entire sample was 75.5 ± 9.1 years (range 39–97). Patients were segregated into age-at-death cohorts as follows: 24 patients <70 years, 26 patients 70–74 years, 36 patients 75–79 years, 27 patients 80–84 years and 16 patients >84 years. Mean maximum levodopa dose was 766 ± 423 mg; there were no significant levodopa treatment differences across the age-at-death groups.

The mean duration of Parkinson's disease was 13.7 ± 7.1 years (range 2–33). There were no significant differences in disease duration between any of the age-at-death groups. In Fig. 1, the disease courses of the cohorts are aligned for age at death and the mean time points for the disability milestones (regular falls, visual hallucinations, cognitive disability and residential care) are indicated. There was little variation in the temporal relationship between each milestone and death across the groupings, and none of the differences were significant. On average, visual hallucinations preceded death by 5.1 years; regular falls by 4.1 years, dementia by 3.3 years, and need for residential care by 3.3 years. The milestone of cognitive disability showed the greatest consistency in time to death across the groups.

In Fig. 2, the sample of 129 cases is divided into five roughly equal groups by age at Parkinson's disease onset, using the same milestones as in Fig. 1, but giving a different perspective of the relationship between age and disease duration. As in Fig. 1, the intervals between milestones and death vary little across the age-at-onset cohorts, but here the effect of age of onset on disease duration is apparent. There was a strong negative correlation between the age at onset and the time to the first milestone (Pearson $R = -0.62$, $P < 0.0001$) and to the mean milestone time-point ($R = -0.62$, $P < 0.0001$). Age at onset showed no

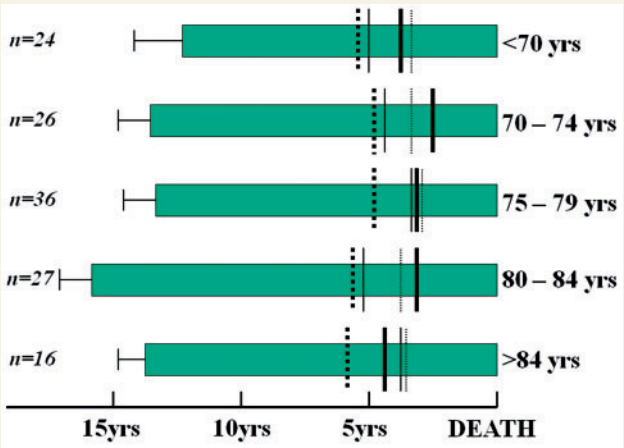

Figure 1 Disease course and disability milestones for the five age-at-death groupings, aligned for time of death. Regular falls = fine lines; residential care = heavy lines; cognitive disability = fine dots; visual hallucinations = heavy dots. Error bars show the standard error of the mean disease duration.

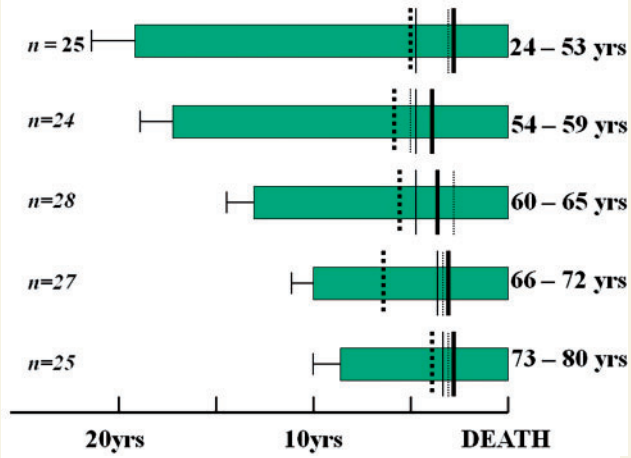

Figure 2 Disease course and disability milestones for five age-at-onset groups. Disease courses aligned for time of death. Same milestone legend as Fig. 1. Error bars show the standard error of the mean disease duration.

significant correlation with the intervals between the first milestone and death, and between the mean milestone time-point and death. Age at death showed no significant correlation with any of these milestone time measurements. Total disease duration was correlated with time from onset to the first milestone ($R = 0.92$, $P < 0.001$) and to the mean milestone time-point ($R = 0.94$, $P < 0.0001$), and less strongly correlated with the time from first milestone to death ($R = 0.30$, $P = 0.002$) and from the mean milestone time-point to death ($R = 0.25$, $P = 0.01$). Multivariate analyses were performed using the Cox regression model in an attempt to identify clinical factors which independently influenced the milestone-free disease duration. For all four milestones, the milestone-free duration depended on the total duration of Parkinson's disease (Cox hazard rate ratio: $P < 0.0005$ for each analysis).

Table 1 contains age demographics, maximum levodopa dosage, and timing and frequency of the milestones according to the age-at-death classification. Visual hallucination was the most frequently recorded milestone (61%), followed by dementia (54%), nursing home placement (43%) and regular falling (35%). Among patients who developed dementia, visual hallucinations were documented in 77%. Milestone frequency was generally lower in the youngest age-at-death group. Regular falls (χ^2: $P = 0.004$), visual hallucinations (χ^2: $P = 0.009$) and nursing home placement (χ^2: $P = 0.04$) were significantly less frequent than the expected rate for all patients aged more than 70 years at death. The difference for dementia frequency between those who died before and after 70 years of age was not significant (χ^2: $P = 0.4$). There were no significant differences in milestone frequency between any other age groups. The milestone of cognitive disability had the most consistent frequency across all groups. There was no significant difference between the maximum levodopa dosage for patient with (745 mg) and without (732 mg) visual hallucinations. Dopamine receptor agonist drugs had been prescribed to 48% of those with visual hallucinations, compared with 50% of those without. Seven patients received negligible dopaminergic therapy during their disease course; six of these had experienced visual hallucinations.

The mean number of milestones documented for the entire sample was 1.9. Fourteen patients had accumulated all four disability milestones before death; 30 had three milestones, 37 reached two, and 29 reached one. There were 19 cases where no milestones were recorded. The youngest age-at-death group contained the highest proportion of zero milestone recording.

Most patients died from the consequences of advanced Parkinson's disease or from intercurrent medical disorders developing late in the course of the illness. There were 12 cases (9%) where the medical records revealed a serious disease not related to Parkinson's disease that caused or strongly contributed to premature death (five from neoplasia, five had cardiovascular disease or sudden cardiac death and two died from stroke). These patients had a relatively short mean disease course of 10.1 ± 5.5 years (range 4–22), although the difference from the rest of the sample was at borderline significance (t-test: $P = 0.06$). They tended to be younger when they died (mean age 71.2 years), and composed 21% of the <70 years at death cohort. Their mean number of milestones was 0.8, compared with a mean of 2.1 for those patients without premature death (t-test: $P = 0.001$). Seven of the 12 premature death patients had no milestones recorded; this was significantly greater than the expected zero milestone rate from the rest of the patient sample (χ^2: $P < 0.0005$).

The pathological findings are shown in Table 2. The mean Lewy body score for the entire sample was 7.3 ± 2.2. The youngest age group had the lowest Lewy body score, although this was not significantly different from all patients who were aged 70 years or greater at time of death (Mann–Whitney U: $P = 0.15$). There was little difference across the older age groups, nor were there significant differences when comparing the Lewy body scores of the youngest to the oldest age-at-death subgroups (Mann–Whitney U: $P = 0.23$). Alzheimer neurofibrillary pathology was reported in 74% of cases. There were no significant differences in the mean neurofibrillary tangle stage or in the prevalence of this pathology across the groups. Substantial amounts of amyloid-β plaques (CERAD age-related plaque scores B–C) were present in 15.5% of the sample; their mean age at death was 76.9 years, compared with 75.3 years for those with low or negligible plaque deposition (t-test: $P = 0.46$). The mean Lewy body score in the 12 cases of premature death from other causes was 5.8 ± 2.4, which was significantly less than for the rest of the sample (7.4 ± 2.2; Mann–Whitney U: $P = 0.03$).

The cognitive disability milestone was associated with a significantly heavier deposition of cerebral cortical Lewy bodies. Mean Lewy body score was 8.0 for demented patients, and 6.4 for non-demented patients (Mann–Whitney U: $P < 0.0005$). Eighty percent of demented patients had neocortical Lewy body disease, compared with 43% for the non-demented cases (χ^2: $P \leq 0.0005$). Those with dementia also had more Alzheimer neurofibrillary pathology (mean neurofibrillary tangle stage 2.5 compared with 1.8, Mann–Whitney U: $P = 0.03$), although the burden of this pathology was mild to moderate in most cases where it was observed. Only five patients, who were all demented, had severe changes (neurofibrillary tangle stage 5–6). Of the

Table 1 Clinical features including disability milestones analysed by age at death

	Age at death <70 years n = 24	Age at death 70–74 years n = 26	Age at death 75–79 years n = 36	Age at death 80–84 years n = 27	Age at death >84 years n = 16
Age at death	61.2 ± 7.3	71.9 ± 1.4	77.3 ± 1.4	81.8 ± 1.3	88.4 ± 3.2
Disease duration	12.3 ± 8.6	13.6 ± 6.2	13.0 ± 7.3	15.9 ± 7.4	13.8 ± 4.4
(range)	(2–27)	(2–29)	(2–28)	(4–33)	(7–33)
Maximum levodopa dose (mg)	833 ± 663	824 ± 360	697 ± 263	761 ± 450	713 ± 273
Regular falls					
Time to death (range)	5.0 (2–11)	4.4 (1–9)	3.2 (1–7)	5.2 (3–7)	3.7 (2–7)
Number (%)	3 (13)	10 (38)	17 (47)	10 (37)	5 (31)
Cognitive disability					
Time to death (range)	3.3 (1–9)	3.4 (1–8)	2.9 (1–7)	3.8 (2–9)	3.6 (2–8)
Number (%)	11 (46)	17 (65)	19 (53)	15 (56)	7 (44)
Visual hallucinations					
Time to death (range)	5.4 (1–15)	4.8 (2–13)	4.7 (2–13)	5.6 (2–12)	5.9 (2–9)
Number (%)	10 (42)	17 (65)	23 (64)	19 (70)	10 (63)
Residential care					
Time to death (range)	3.7 (1–8)	2.6 (1–6)	3.1 (1–9)	3.1 (1–7)	4.3 (1–8)
Number (%)	6 (25)	9 (35)	18 (50)	15 (56)	8 (50)

Data are mean ± standard deviation.

Table 2 Pathological data analysed by age at death

	Age at death <70 years n = 24	Age at death 70–74 years n = 26	Age at death 75–79 years n = 36	Age at death 80–84 years n = 27	Age at death >84 years n = 16
Lewy body score	6.7 ± 2.2 Mann–Whitney *U*: $P = 0.15$	7.8 ± 2.2	7.1 ± 2.2	7.2 ± 2.1	7.6 ± 2.5
Neocortical Lewy body disease, number (%)	12 (50) χ^2: $P = 0.08$	16 (62)	23 (64)	17 (63)	12 (75) χ^2: $P = 0.13$
Neurofibrillary tangle stage	1.9 ± 1.8	2.2 ± 1.4	2.3 ± 1.0	2.4 ± 0.9	2.3 ± 1.2
Neurofibrillary pathology prevalence, number (%)	16 (67)	16 (62)	29 (81)	21 (78)	13 (81)

Data are mean ± standard deviation. Statistical analyses refer to age-at-death group results compared with all other age groups combined.

20 cases with CERAD age-related amyloid-β plaque scores of B or C, 17 were demented (χ^2: $P = 0.007$). Four fulfilled the CERAD criteria for a definite neuropathological diagnosis of Alzheimer's disease. Patients with visual hallucinations had significantly higher Lewy body scores (7.7) than those without (6.6; Mann–Whitney *U*: $P = 0.02$). The Lewy body score correlation was at borderline significance for nursing home placement (7.7 versus 7.0; Mann–Whitney *U*: $P = 0.054$) and weaker for regular falls (7.6 versus 7.1; Mann–Whitney *U*: $P = 0.33$).

There was a correlation between the accumulation of multiple milestones and the mean Lewy body score (Spearman's rho, correlation coefficient = 0.36, $P \leq 0.0005$). Figure 3 shows the Lewy body burden according to milestone number. Alzheimer neurofibrillary pathology scores did not significantly correlate with the accumulation of clinical milestones (Pearson correlation: $P = 0.14$).

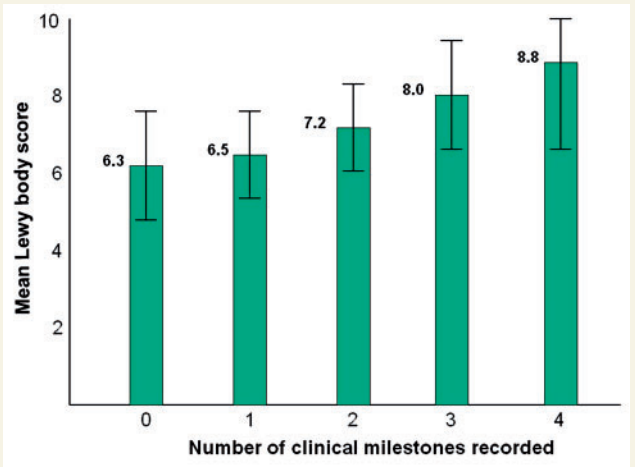

Figure 3 Lewy body scores according to number of milestones accumulated. Error bars show the standard error of the mean.

Discussion

We have focussed on the late phase of Parkinson's disease by identifying four clinical events that are recognized as markers of severe handicap. Medical records compiled by working clinicians have a problem-orientated focus, and can generally be relied upon to document such developments. Dementia and nursing home placement are common to the late phase of a number of neurodegenerative disorders, but each of the chosen milestones has a

clear significance when reached during the course of Parkinson's disease. Figure 1, which segregates patients according to age at death, shows that the milestones have a common pattern, irrespective of the age at which they occur. Their timing reflects proximity to the end of the disease rather than age, and the order in which they appear is generally the same. Visual hallucination, which preceded death by about 5 years, was often the first sign of advanced disease stage. Cognitive impairment had the greatest consistency in time to death across all of the groupings. At first glance, the finding that the total disease duration does not vary according to age at death seems surprising. However, the youngest age-at-death group selected young onset cases with relatively malignant disease courses; those patients with slower rates of progression tended to survive to an older age. Figure 2 helps to reconcile our findings with clinical studies in which the effects of age on progression are clearly discernible. Young onset Parkinson's disease is associated with a long disease course, motor fluctuations, dyskinesia and, in comparison with older onset patients, preservation of cognition (Schrag *et al.*, 1998). Prospective studies show a relationship between age and cognitive decline, with particular susceptibility above 70 years of age (Williams-Gray *et al.*, 2007; Buter *et al.*, 2008). Figure 2 shows the longer disease course of the younger onset cases, but a similar milestone to death time across the groups. These impressions are supported by the strong correlations between total disease duration and the time between onset and milestones, and also by the multivariate analysis of milestone-free time. Taken together, Figs 1 and 2 suggest that the clinical disease can be subdivided into a variable early–middle phase that precedes the milestones, followed by a more stereotyped late period of milestone accumulation. Age appears to influence the rate at which the early and middle stages progress. On average, younger onset cases take longer to reach the point of cognitive decline. The milestones then usher in the terminal stage, and death is preceded by a period of increasing physical and cognitive disability that runs a similar time course at whatever age it starts.

Similarities in the clinical features of the advanced disease state were mirrored by the scores for cortical Lewy bodies across the age-at-death groups. The youngest group had a slightly lower Lewy body score, which was not statistically significant. For the four cohorts who died after age 70 years, there was no noticeable age effect on Lewy body burden at all. Overall, the amount of Alzheimer neurofibrillary pathology was moderate. Neither the grading nor the prevalence of this pathology showed significant correlation with age at death. There was no significant link between age at death and the deposition of higher grades of amyloid-β plaques. The relationship between the clinical milestones and Lewy body pathology was strongest for the dementia milestone, and for visual hallucination, which was often associated with dementia. Physical disability would not be expected to correlate as strongly with cortical Lewy body deposition, and the link with the residential care and falling milestones is weaker. As shown in Fig. 3, the accumulation of multiple milestones is a strong predictor of higher Lewy body scores, in direct proportion to the number of milestones recorded. In the group who died from other medical disorders at an earlier stage of the disease course, low milestone accumulation was associated with a low mean Lewy body score. All of this evidence supports a link between Lewy body burden and the clinical manifestations of advanced Parkinson's disease.

Our observation that there is a strong correlation between dementia and Lewy body score concurs with studies such as Saito *et al.* (2004) and Braak *et al.* (2005). Visual hallucinations have been shown to relate to Lewy body density in the temporal lobes (Harding *et al.*, 2002). But other research suggests more variable clinical associations with Lewy body deposition. Not all patients with Parkinson's disease with widespread cortical Lewy body lesions become demented (Colosimo *et al.*, 2003), and 55% of subjects who had widespread alpha-synuclein deposits (equivalent to neocortical Braak stages 5–6) in one large autopsy series were not known to have had either dementia or extrapyramidal impairment in life (Parkkinen *et al.*, 2008). It should be stated that 83% of the cases reported by Parkkinen *et al.* (2008) from the Kuopio Brain Bank did display the caudorostral gradation of alpha-synuclein pathology predicted by Braak. Some authors disagree with the Braak assertion that these intracellular inclusions are proportionately related to neurodegeneration and death. Parkkinen and colleagues for example have suggested an inverted U-shape plot of substantia nigra Lewy body density against time (Parkkinen *et al.*, 2008), and Greffard *et al.* (2010) found a consistent proportion of 3–4% of Lewy body-containing substantia nigra neurons in Parkinson's disease, regardless of disease stage (Greffard *et al.*, 2010). We also found significantly greater amounts of Alzheimer's disease related neurofibrillary and amyloid-β plaque pathology in demented cases. Other studies have suggested that alpha-synuclein, tau and amyloid-β deposition in the limbic regions may have an additive effect in causing cognitive impairment (Kalaitzakis *et al.*, 2009). Halliday *et al.* (2008) found a proportion of rapidly progressive cases with high loads of Lewy bodies associated with plaque formation, and suggested possible overlapping cellular mechanisms for these pathologies. Amyloid-β protein deposition could act synergistically to increase alpha-synuclein aggregation in Lewy body disorders (Pletnikova *et al.*, 2005; Lashley *et al.*, 2008).

In general, our clinico-pathological observations on the milestones of the advanced disease state do support a pathological staging system based on the rostral extent and severity of Lewy body pathology. There were some individuals in whom high Lewy body scores were not associated with dementia or multiple milestone accumulation. But in clinically well-documented cases of Parkinson's disease, we have shown that, in contrast to the conclusions that Parkkinen *et al.* (2008) drew from a large general autopsy series, there is a good correlation between alpha-synuclein deposition and clinical disability. The most contentious aspects of the Braak model of stages of Parkinson's disease concern its predictions regarding pre-clinical and early clinical disease pathology, on which we make no statement except to remark on the difficulties in inferring longitudinal pathological information from cross-sectional surveys of end-stage pathology. When it comes to the final phase of the clinical disease, our findings show that, here at least, the two Braak postulates appear to hold true: progression occurs according to factors that are intrinsic to the pathology itself, and there is little influence from age on clinical and pathological measures of late Lewy body deposition.

Further explanation is needed to account for the variable early–middle and the fixed late portions of the disease course, and for the differential effects of age. One possibility is that clinical disease progression is governed by an exponential rather than a linear time relationship, as represented schematically in Fig. 4. According to this graph, the effect of age produces a longer disease course in the younger onset cases. Once the advanced disease stage is reached, progression speeds up to match that of the older onset cases. This upward curving relationship could occur because the pathological process of Parkinson's disease itself accelerates at a certain point. But the simple mathematics of neuronal populations in the central nervous system does suggest another hypothesis. Our findings are consistent with the notion that the clinical phase of Parkinson's disease is associated with upward spreading of Lewy body pathology from the midbrain. If successive anatomical sites are involved with a roughly linear time relationship, the number of neurons affected would rise exponentially, since the regional transition from brainstem nuclei to transentorhinal cortex to the neocortex involves neuronal populations that increase by orders of magnitude at each stage. This might cause a pathological process governed by linear factors to have apparently exponential clinical effects.

Our observations have some practical applications. Visual hallucinations, frequent falling and early cognitive decline should be absolute contraindications for deep brain stimulation surgery, or for cell-based therapies focussing on the nigrostriatal dopamine system. A more benign prognosis should not be assumed when these milestones occur in relatively youthful patients. In a more general sense, this perspective of the entire disease course contributes to strategic thinking on pharmacological treatment. The appearance of the milestones represents a major challenge for pharmacological intervention and a reconsideration of the treatment advised for motor handicap. In clarifying the relationship between the final disease phase, the pre-milestone period and age, we emphasize the years of best opportunity for benefit from dopaminergic treatment. Lastly, a clearer understanding of the relationship between age and progression of Parkinson's disease should assist clinical trial design and patient selection for future assessments of potential disease modifying therapies.

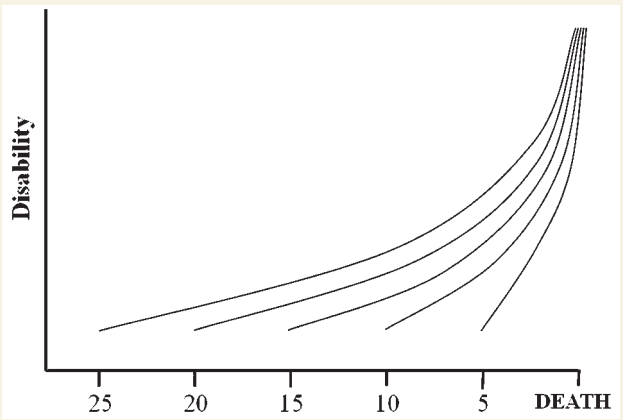

Figure 4 Schematic representation of exponential clinical progression over different disease durations, with clinical disability plotted against disease course in years.

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