Clinical outcomes of progressive supranuclear palsy and multiple system atrophy

S. S. O'Sullivan,[1,2] L. A. Massey,[2,3] D. R. Williams,[1,4] L. Silveira-Moriyama,[1,2] P. A. Kempster,[5] J. L. Holton,[2] T. Revesz[2] and A. J. Lees[1,2,3]

[1]Reta Lila Weston Institute of Neurological Studies, Institute of Neurology, [2]Queen Square Brain Bank for Neurological Disorders and Institute of Neurology, [3]Sara Koe PSP Research Centre, Institute of Neurology, University College London, London, UK, [4]Faculty of Medicine (Neuroscience), Monash University (Alfred Hospital Campus) and [5]Department of Neurosciences, Monash Medical Centre, Melbourne, Australia

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

Prognostic predictors have not been defined for progressive supranuclear palsy (PSP) and multiple system atrophy (MSA). Subtypes of both disorders have been proposed on the basis of early clinical features. We performed a retrospective chart review to investigate the natural history of pathologically confirmed cases of PSP and MSA. Survival data and several clinically relevant milestones, namely: frequent falling, cognitive disability, unintelligible speech, severe dysphagia, dependence on wheelchair for mobility, the use of urinary catheters and placement in residential care were determined. On the basis of early symptoms, we subdivided cases with PSP into 'Richardson's syndrome' (RS) and 'PSP-parkinsonism' (PSP-P). Cases of MSA were subdivided according to the presence or absence of early autonomic failure. Sixty-nine (62.7%) of the 110 PSP cases were classified as RS and 29 (26.4%) as PSP-P. Of the 83 cases of MSA, 42 (53.2%) had autonomic failure within 2 years of disease onset. Patients with PSP had an older age of onset ($P < 0.001$), but similar disease duration to those with MSA. Patients with PSP reached their first clinical milestone earlier than patients with MSA ($P < 0.001$). Regular falls ($P < 0.001$), unintelligible speech ($P = 0.04$) and cognitive impairment ($P = 0.03$) also occurred earlier in PSP than in MSA. In PSP an RS phenotype, male gender, older age of onset and a short interval from disease onset to reaching the first clinical milestone were all independent predictors of shorter disease duration to death. Patients with RS also reached clinical milestones after a shorter interval from disease onset, compared to patients with PSP-P. In MSA early autonomic failure, female gender, older age of onset, a short interval from disease onset to reaching the first clinical milestone and not being admitted to residential care were independent factors predicting shorter disease duration until death. The time to the first clinical milestone is a useful prognostic predictor for survival. We confirm that RS had a less favourable course than PSP-P, and that early autonomic failure in MSA is associated with shorter survival.

Introduction

Progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) are the most common causes of neurodegenerative-parkinsonism, after Parkinson's disease (PD), with an estimated prevalence for PSP of 6.4 per 100 000 and for MSA of 4.4 per 100 000. (Schrag *et al.*, 1999) MSA may be divided into clinical subtypes, according to whether cerebellar (MSA-C) or parkinsonian (MSA-P) symptoms predominate (Gilman *et al.*, 1999) and a recent study has demonstrated that early autonomic dysfunction may also be a prognostic indicator in MSA (Tada *et al.*, 2007). We have previously shown that PSP may be classified into two major clinical subtypes, 'Richardson's syndrome' (RS) and 'PSP-parkinsonism' (PSP-P) (Williams *et al.*, 2005).

The two published large natural history studies of PSP are limited by the low rate of pathological confirmation of the diagnosis (Nath *et al.*, 2003; Golbe and Ohman-Strickland, 2007). With the exception of a meta-analysis of 108 papers by Wenning *et al.*, (Wenning *et al.*, 1997) the few large natural history studies in MSA also lack pathological confirmation, with only 22 of the 230 patients described by Watanabe coming to autopsy (Watanabe *et al.*, 2002). Prospective clinical studies have to contend with diagnostic uncertainty and selection bias, making analysis of disease progression and the factors that predict prognosis difficult. We have attempted to overcome some of these shortcomings of past research by evaluating a large series of pathologically confirmed cases of PSP and MSA.

PSP and MSA are commonly mistaken for one another in clinical practice (Hughes *et al.*, 2002). Because of difficulties distinguishing one from the other, physicians often use the imprecise all embracing terms 'atypical Parkinsonism' or 'Parkinson's-plus' syndromes. This study aims to compare and contrast the clinical features that predict prognosis of PSP and MSA, using a number of relevant disability milestones in addition to survival data. We also aim to further analyse subgroups of these conditions based on early clinical features, to improve the prognostic ability of treating physicians.

Methods
Patients
Patients with a pathological diagnosis of PSP and MSA were identified from the archives of the Queen Square Brain Bank for Neurological Disorders (QSBB). All cases that came to autopsy over a 20-year period (1987 and 2007) were included. Some of the cases have been included in previous reports from the QSBB (previously known as the Parkinson's Disease Society Brain Research Centre); (Fearnley and Lees, 1990; Hughes *et al.*, 1991, 1992; Wenning *et al.*, 1994*a*, *b*; Daniel *et al.*, 1995; Wenning *et al.*, 1995, 2000; Hughes *et al.*, 2002; Morris *et al.*, 2002; Gibb *et al.*, 2004; Ozawa *et al.*, 2004; Williams *et al.*, 2005). The research presented in this study was approved by the Joint Research Ethics Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology.

The diagnosis of PSP was made according to the National Institute for Neurological Diseases and Stroke-Society for PSP (NINDS-SPSP) neuropathological criteria (Hauw *et al.*, 1994; Litvan *et al.*, 1996*a*), and the diagnosis of MSA was made according to established neuropathological criteria (Papp *et al.*, 1989; Lowe, 1997). Diagnostic criteria were applied retrospectively to those cases acquired prior to the publication of the criteria.

Medical record review
We performed a systematic review of the case files, including the comprehensive case notes of the family doctor and all of the correspondence between the family doctor and the medical specialist. All patients had been assessed by hospital specialists (neurologists or geriatricians) throughout the course of their illness. The information gleaned from the case notes was independently assessed by two neurologists who were blinded to the pathological diagnosis. Cases were excluded if the medical records did not contain regular and well-documented statements of the disease progression.

A clinical data sheet was designed to record the presence or absence of clinical features either early in the disease course (within 2 years of first symptom onset) or at any time later in the disease (Williams *et al.*, 2005). Symptoms were recorded as being absent if not reported, and clinical signs were recorded separately as unknown if they were not specifically mentioned in the notes. Where conflicting clinical features were reported, the findings of the neurologist were used.

Definitions were as follows (i) Age of onset: age, in years, at the time of the first reported symptom considered to be attributable to MSA or PSP (ii) Duration: time between the age of onset and the age at death (iii) Autonomic dysfunction: either abnormal autonomic function testing or documentation of any two of the following symptoms reported by patients: urinary urgency, frequency and nocturia without hesitancy; chronic constipation; postural hypotension; sweating abnormalities or erectile dysfunction. Asymptomatic postural hypotension on clinical examination (defined as a >20 mm systolic blood pressure drop on standing for 2 min) was also included as evidence of autonomic dysfunction. (iv) Response to levodopa: a reported improvement of >30% coincident with the introduction of levodopa was recorded as being a positive response. A 4-point scale modified from the QSBB annual assessment forms graded this degree of response. In most cases, the degree of response to levodopa was based on the clinical impression documented by the treating physician, with specific changes in formal rating scales of parkinsonism such as the Unified Parkinson's Disease Rating Scale, or functional ratings such as the Barthel's index of activities of daily living, being less frequently documented. Formal ratings of improvement post-levodopa were approximated with clinical impressions as follows: 1 = nil, or <30% improvement; 2 = moderate response (30–50% improvement); 3 = good response (51–70% improvement); and 4 = excellent response (71–100% improvement). A sustained response to levodopa was defined as a reported benefit after 2 years from commencement of levodopa.

Seven milestones of disease progression were selected on the basis that all were likely to require additional medical attention, and to be well documented in the medical records. These were: frequent falling (defined as falls occurring more than twice per year, or the documentation of 'frequent' or 'regular' falls), cognitive disability, unintelligible speech or the requirement of communication aids, severe dysphagia or the offering of percutaneous endoscopic gastrostomy (PEG) tube placement for feeding, dependence on wheelchair for mobility, the use of urinary catheters and placement in residential or nursing home care. The year of onset or occurrence of each milestone was noted. When the onset was not recorded, we noted the time that the symptom was first mentioned in the case notes. Significant cognitive impairment was defined as substantial and apparently permanent impairment of ability to perform tasks of daily living because of cognitive disability. (DSM-IV, 1995)

Clinical subdivision of PSP and MSA cases
The PSP cases were subdivided into the two clinical phenotypes: RS and PSP-P. (Williams *et al.*, 2005) These groups were assigned according to the number of clinical features present in the first

Table 1 Comparison of clinical features in the different disease groups

	PSP versus MSA			PSP subtypes			MSA subtypes		
	PSP	MSA	*P*	RS	PSP-P	*P*	With EAS	Without EAS	*P*
Number of cases	110	83		69	29		42	37	
Percentage of Female (*n*)	37% (41)	55% (46)	0.013*	32% (21)	54% (14)	NS	40% (17)	70% (26)	0.012*
Age of onset Mean ± SD	65.6 ± 8.4	56.8 ± 10.2	<0.001†	66.5 ± 7.4	63.2 ± 9.9	NS	54.7 ± 9.5	58.1 ± 10.2	NS
Time between onset and diagnosis Mean ± SD	3.5 ± 2.6	3.7 ± 2.5	NS	3.1 ± 2.0	4.0 ± 3.7	NS	3.7 ± 2.3	4.0 ± 2.7	NS
Disease duration Mean ± SD	8.0 ± 4.1	7.9 ± 2.8	NS	6.3 ± 2.4	11.7 ± 4.9	<0.001†	7.2 ± 2.7	8.8 ± 2.7	0.014†
Age at death Mean ± SD	73.8 ± 8.1	64.7 ± 9.0	*P* <0.001†	72.8 ± 7.1	74.9 ± 9.3	NS	61.9 ± 8.0	66.9 ± 8.9	0.01†
Percentage of Patients with correct clinical diagnosis of PSP or MSA	72%	70%	NS	86%	41%	<0.001*	88%	54%	0.001*
Percentage of patients (*n*) responsive to L-Dopa	33.7% (28)	62.9% (44)	0.001*	17% (8)	65.5% (19)	<0.001*	62.5% (20)	61.1% (22)	NS
L-dopa response Mean ± SD	1.2 ± 0.9	1.9 ± 1.0	<0.001†	0.9 ± 0.6	2.0 ± 0.9	<0.001†	1.7 ± 1.0	2.1 ± 1.0	NS
Percentage of of patients with sustained response to L-Dopa >2 years	18 (27.7%)	24 (34.3%)	NS	5 (10.6%)	12 (41.4%)	0.004*	12 (37.5%)	10 (27.8%)	NS

NS = non-significant, EAS = early autonomic symptoms.
*Chi Squared test, †Student's *t*-test.

2 years of disease. When falls, cognitive dysfunction, supranuclear gaze palsy, abnormalities of saccadic eye movements and postural instability were the predominant clinical features, patients were categorized as RS. PSP-P was considered when bradykinesia or tremor, levodopa response, asymmetric onset and limb dystonia dominated the clinical picture in the first 2 years (Williams *et al.*, 2005). When features of both groups were equal in the first 2 years patients were grouped as 'unclassifiable'.

In cases of MSA, we compared those patients presenting with symptoms and signs of autonomic dysfunction within the first 2 years from disease onset. Because of referral bias to the QSBB, which specializes in parkinsonian disorders, the vast majority of MSA cases were of the MSA-P subtype. Therefore, comparisons between MSA-P and MSA-C were not possible.

Statistical analysis

Clinical details including age at disease onset, age at death, disease duration were compared between patient groups. Mean results and comparisons for each milestone of advanced disease refer only to those patients in whom one of these event occurred. Univariable analyses using χ^2 for categorical and two-tailed *t*-test or the Mann–Whitney U-test, as appropriate, for continuous variables were applied. The interval in years from first symptom onset to each clinical milestone or death was graphically assessed using Kaplan-Meier curves, and curves from each patient subgroup were compared with the log rank test. Cox multiple stepwise regression analysis was performed in MSA and PSP for disease duration, using clinical factors present around disease onset (within the first 2 years), the presence of clinical milestones and gender as categorical covariates, with age at onset and the interval from disease onset to reaching each clinical milestone as continuous variables. Statistical analyses of data were performed with SPSS version 12.0 (SPSS, Chicago, IL).

Results
Patient characteristics
We identified 123 cases of PSP and 93 cases of MSA for review. Twenty-three of these (13 PSP, 10 MSA) were excluded because of inadequate information in the medical records.

Of the 110 cases of PSP, 69 (62.7%) had RS and 29 (26.4%) PSP-P. Of the PSP, 12 (10.9%) cases were unclassifiable because of incomplete documentation of the initial presenting symptoms, or equal numbers of symptoms in the 'RS' and 'PSP-P' criteria. Of the 83 cases of MSA, 42 (53.2%) had documented autonomic failure within 2 years of disease onset.

A higher proportion of RS (86%) patients than PSP-P (41%) cases were diagnosed accurately during life as having PSP (χ^2, *P* <0.001). Patients with early autonomic dysfunction were more likely to be diagnosed during life with MSA (χ^2, *P* = 0.001). A higher proportion of males were seen amongst the cases of MSA with early autonomic dysfunction (male : female 1.5 : 1.0), than in the group of patients without early autonomic dysfunction (0.4 : 1.0, χ^2, *P* = 0.0012). Clinical features were compared between cases with MSA or PSP, in addition to comparisons between clinical subgroups of MSA and PSP in Table 1.

Survival comparisons between patient groups

Patients with PSP were older at disease onset than those with MSA, (*t*-test, *P* <0.001), but disease duration was similar. See Table 1, and Fig. 1A–E for Kaplan-Meier survival curves. RS and PSP-P groups had similar mean ages of disease onset, however, patients with RS had
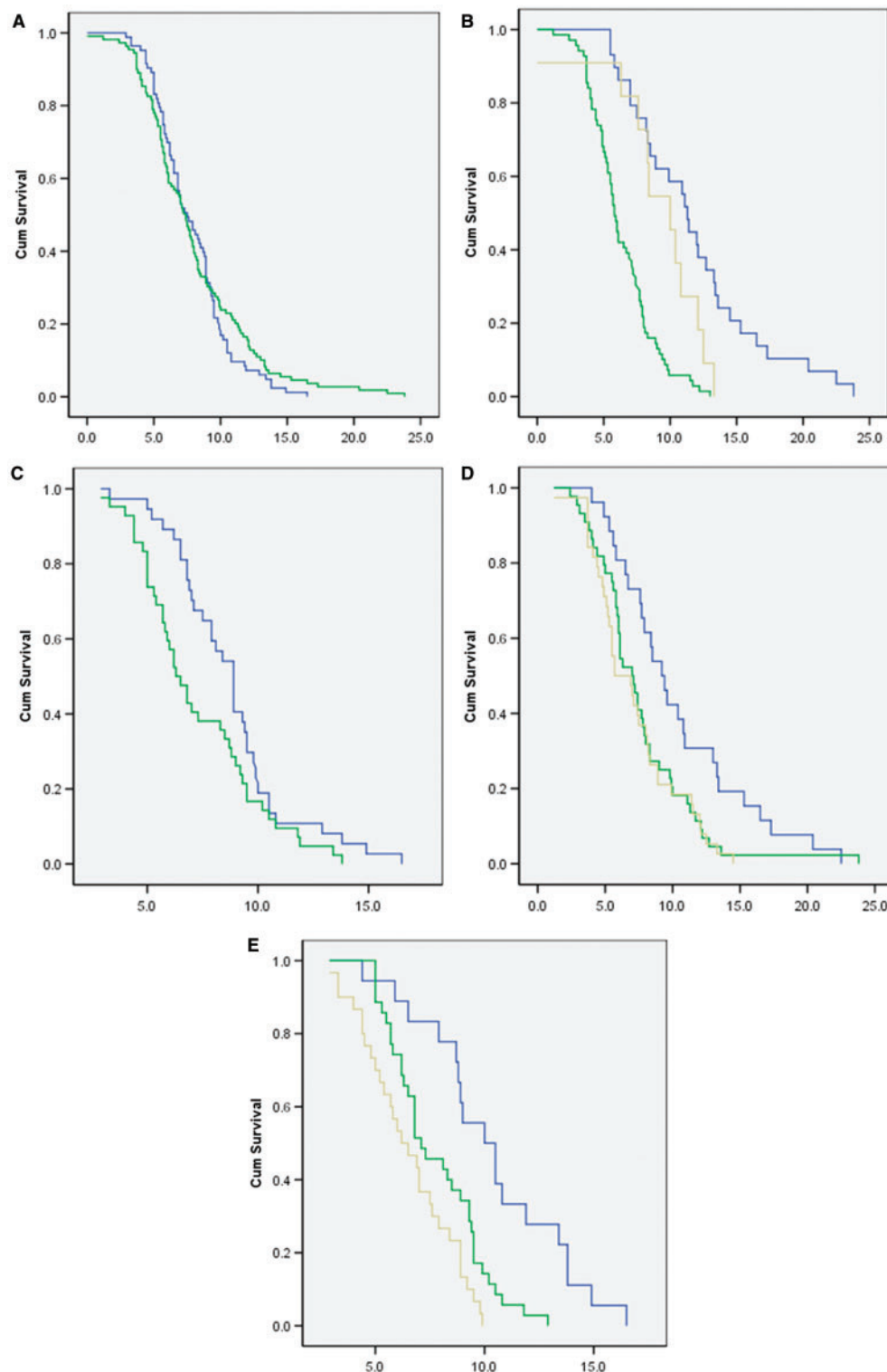
Fig. 1 Kaplan-Meier survival curves from symptom onset according to clinical subtypes. (**A**) Interval from disease onset to death in PSP and MSA (years). Log Rank (Mantel-Cox) df = 1, $P = 0.5$. PSP, green doted line; MSA, blue dotted line. (**B**) Interval from disease onset to death in PSP subtypes (years). Log Rank (Mantel-Cox), df = 2, $P = 0.000$. RS, green doted line; PSP-P, blue dotted line; Unclassified, Yellow dotted line. (**C**) Interval from disease onset to death in MSA subtype (years). Log Rank (Mantel-Cox), df = 1, $P = 0.037$. Early autonomic dysfunction, green dotted line; No early autonomic dysfunction, blue dotted line. (**D**) Interval from disease onset to death in PSP subtype (years) according to the age of symptom onset. Log Rank (Mantel-Cox), df = 2, $P = 0.011$ <60-years-old, blue dotted line; 60- to 69.9-year-old, green dotted line; >70-years-old, yellow dotted line. (**E**) Interval from disease onset to death in MSA subtype (years) according to the age of symptom onset. Log Rank (Mantel-Cox), df = 2, $P = 0.000$. Less than 50-years-old, blue dotted line; 50- to 59.9-years-old, green dotted line; >60-years-old, yellow dotted line.

Table 2 Independent predictors of disease duration in PSP and MSA from the Cox multiple regression analysis on early clinical features, age and sex

|	HR	95% CI	P-value
PSP			
RS phenotype	2.37	1.21–4.64	0.01
Age of onset	1.05	1.02–1.1	0.005
Male gender	1.7	1.03–2.91	0.038
Interval between disease onset and reaching first clinical milestone	0.8	0.71–0.9	<0.001
MSA			
Not admitted to residential care	2.8	1.45–5.46	0.002
Early Autonomic dysfunction	6.0	3.1–11.7	<0.001
Age of onset	1.05	1.02–1.1	0.003
Female gender	3.0	1.7–5.4	<0.001
Interval between disease onset and reaching first clinical milestone	0.58	0.49–0.68	<0.001

a shorter disease duration than those with PSP-P [*t*-test $P < 0.001$, Log Rank (Mantel-Cox), $P < 0.001$]. Patients with MSA and early autonomic dysfunction had similar mean ages of disease onset, but had a shorter disease duration [*t*-test, $P = 0.0014$, Log Rank (Mantel-Cox), $P = 0.037$], than those patients without early autonomic dysfunction. Figure 1D–E describe survival curves in PSP and MSA according to the age of disease onset.

Multivariate analyses performed using the Cox multiple stepwise regression model identified several clinical factors that independently influence disease duration. In PSP an RS phenotype, male gender, older age of onset and a short interval from disease onset to reaching the first clinical milestone were all independent predictors of shorter disease duration until death. In MSA early autonomic dysfunction, female gender, older age of onset, a short interval from disease onset to reaching the first clinical milestone and not being admitted to residential care were independent factors predicting shorter disease duration until death (Table 2). In the UK, males aged 65 have a life expectancy of 16.9 years, which is 2.8 years less than females at this age (Office of National Statistics, 2007). Whilst these gender differences may partially explain the reduction of life expectancy in males compared with females with PSP by 5.6 years, they cannot account for gender differences seen in MSA.

A grading of the response to levodopa was possible in 82 (75%) of patients with PSP, and in 70 (74%) of those with MSA. When analysed as a multivariate predictor of outcome in PSP and MSA, neither the grade of response, nor the presence of a sustained response were significant.

Clinical milestones—comparison between PSP and MSA

Of the patients, 93% had at least one recorded clinical milestone, with similar mean number of clinical milestones per patient seen in PSP (2.8 ± 1.5) and MSA (2.7 ± 1.6) (Fig. 2). Those patients who had disease
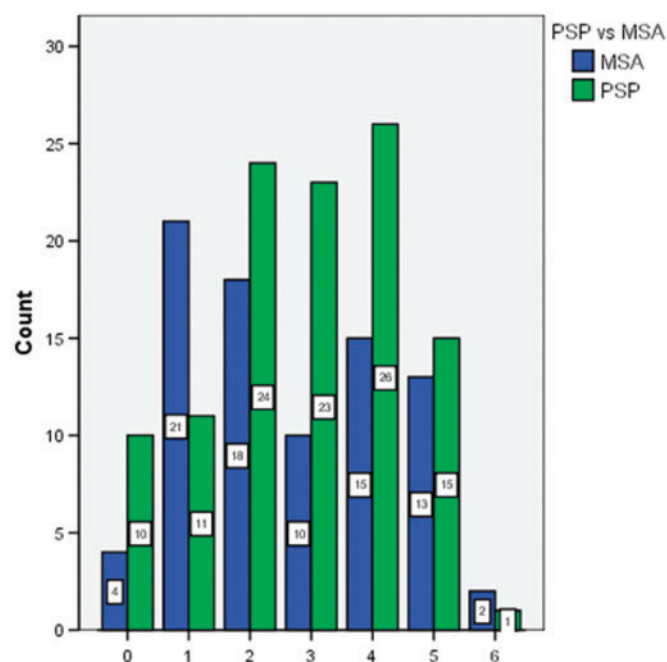
Fig. 2 Number of clinical milestones per patient prior to death according to diagnosis.

durations of $\geqslant 10$ years also had a mean number of milestones of 2.5 ± 1.6 per person. Frequent falls was the most common first milestone in both PSP (63.6%) and MSA (39.3%). In PSP, the next most frequent first milestone was cognitive impairment (15.4%) whereas in MSA it was urinary catheterization (29.4%). Approximately 10% of patients in both groups reached more than one 'first milestone' simultaneously. Patients with PSP reached their first milestone earlier in the disease (mean 3.9 ± 2.7 years), than patients with MSA [5.3 ± 2.2 years; *t*-test, $P < 0.001$, Log Rank (Mantel-Cox), $P = 0.004$]. PSP patients reached most clinical milestones earlier than MSA, except urinary catheterization (See Table 3 and Fig. 3). Figure 4 shows the timing of the clinical milestones of disease advancement and total disease course in MSA and PD, compared with 97 PD cases from the QSBB database (Kempster *et al.*, 2007).

Clinical milestones—comparison between PSP subtypes

Patients with RS reached their first clinical milestone earlier than PSP-P [*t*-test, $P < 0.001$ Log Rank (Mantel-Cox), $P < 0.001$]. More patients with RS developed frequent falls (χ^2, $P = 0.001$), significant cognitive impairment (χ^2, $P = 0.005$) and severe dysphagia (χ^2, $P = 0.02$) than patients with PSP-P. Wheel chair dependence and residential care occurred in equally as often in patients with RS and PSP-P, but time to these milestones was shorter in RS (Table 3).

Table 3 Comparison of number of patients and time to reach milestones of disease advancement in the different disease groups

	PSP versus MSA			PSP subtypes			MSA subtypes		
	PSP	MSA	P	RS	PSP-P	P	With EAS	Without EAS	P
Frequent falls:									
N (%)	84 (82%)	47 (59%)	0.001*	60 (92%)	15 (60%)	0.001*	22 (55%)	23 (64%)	NS
Years from disease onset	3.9 ± 2.5	5.5 ± 2.2	<0.001†	2.9 ± 1.5	6.0 ± 3.0	0.002†	5.7 ± 2.2	5.4 ± 2.4	NS
Years to death mean ± SD	3.8 ± 2.4	2.8 ± 2.0	0.01†	3.1 ± 2.5	2.5 ± 3.2	NS	1.9 ± 1.5	3.8 ± 2.0	0.002
Wheelchair dependant:									
N (%)	48 (46%)	43 (54%)	NS	32 (47%)	13 (50%)	NS	23 (55%)	19 (56%)	NS
Years from disease onset	6.4 ± 2.7	6.7 ± 2.2	NS	5.2 ± 1.9	9.1 ± 2.6	<0.001†	6.6 ± 2.5	6.9 ± 1.8	NS
Years to death mean ± SD	1.6 ± 1.2	1.4 ± 1.3	NS	0.7 ± 1.1	0.8 ± 1.3	NS	1.1 ± 1.1	1.9 ± 1.4	0.04†
Unintelligible speech:									
N (%)	39 (38%)	34 (41%)	NS	28 (44%)	6 (23%)	NS	14 (33%)	19 (53%)	NS
Years from disease onset	6.0 ± 2.5	7.2 ± 2.0	0.04	5.7 ± 2.3	7.0 ± 3.9	NS	6.7 ± 2.0	7.6 ± 2.0	NS
Years to death: mean ± SD	1.5 ± 1.5	1.7 ± 1.6	NS	0.5 ± 0.9	0.7 ± 1.7	NS	1.7 ± 1.4	1.8 ± 1.7	NS
Severe dysphagia:									
N (%)	35 (33%)	26 (32%)	NS	28 (42%)	4 (15%)	0.02*	13 (32%)	12 (33%)	NS
Years from disease onset	6.4 ± 2.4	7.2 ± 2.3	NS	5.9 ± 1.9	9.4 ± 3.8	NS	7.1 ± 2.4	7.6 ± 2.3	NS
Years to death: mean ± SD	1.0 ± 1.1	1.4 ± 1.2	NS	0.4 ± 0.7	0.2 ± 0.9	NS	0.9 ± 0.8	2.0 ± 1.3	0.02†
Urinary catheter:									
N (%)	27 (26%)	49 (60%)	<0.001*	18 (27%)	6 (23%)	NS	29 (71%)	18 (50%)	NS
Years from disease onset	6.3 ± 3.1	6.1 ± 2.6	NS	5.4 ± 2.7	8.3 ± 3.2	NS	5.8 ± 2.7	6.9 ± 2.3	NS
Years to death: mean ± SD	1.2 ± 1.1	1.9 ± 1.7	0.02†	0.3 ± 0.8	0.2 ± 0.6	NS	1.9 ± 1.5	2.1 ± 2.0	NS
Cognitive impairment:									
N (%)	54 (52%)	11 (14%)	<0.001*	41 (62%)	7 (28%)	0.005*	5 (13%)	5 (14%)	NS
Years from disease onset	4.2 ± 2.9	6.2 ± 2.4	0.03†	3.7 ± 2.4	6.5 ± 4.7	NS	6.6 ± 2.5	6.6 ± 2.0	NS
Years to death: mean ± SD	2.4 ± 1.8	1.1 ± 1.1	0.005†	1.4 ± 1.9	0.5 ± 1.0	0.001†	0.9 ± 0.5	0.8 ± 1.2	NS
Residential care:									
N (%)	27 (26%)	14 (18%)	NS	19 (28%)	5 (19%)	NS	5 (12%)	9 (25%)	NS
Years from disease onset	6.1 ± 3.0	7.9 ± 3.3	NS	4.8 ± 2.0	9.9 ± 2.2	0.003†	9.0 ± 2.0	7.3 ± 3.8	NS
Years to death: mean ± SD	1.8 ± 1.3	2.1 ± 1.8	NS	0.4 ± 0.7	0.5 ± 1.3	NS	0.8 ± 0.6	2.7 ± 1.9	0.02†
First milestone:									
N (%)	100 (91%)	79 (95%)	NS	68 (99%)	20 (69%)	<0.001*	40 (95%)	35 (95%)	NS
Years from disease onset	3.9 ± 2.7	5.3 ± 2.2	<0.00†	2.8 ± 1.7	6.2 ± 2.9	<0.001†	5.4 ± 2.4	5.4 ± 2.1	NS
Years to death: mean ± SD	3.7 ± 2.2	2.6 ± 1.9	0.001†	3.5 ± 2.1	4.4 ± 2.8	NS	2.0 ± 1.5	3.4 ± 2.2	0.002†

N = number of patients in the disease group that reached the referred milestone, NS = non-significant, EAS = early autonomic symptoms. *Chi Squared test; †Student's t-test.

Clinical milestones—comparison between MSA subtypes

No difference was seen in the proportion of patients with MSA reaching clinical milestones, or in the intervals from disease onset to these milestones, when this group is divided according to the presence of early autonomic dysfunction.

Discussion

Previous studies investigating the natural history of PSP, (Papapetropoulos et al., 2005), (Golbe et al., 1988; Nath et al., 2003) and MSA (Klockgether et al., 1998; Watanabe et al., 2002) have identified clinical features potentially associated with worse prognoses. To our knowledge this study is the first natural history study supported by pathological diagnostic confirmation in all cases. We found that patients with PSP had a significantly later age

of onset than those with MSA, had more rapid progression to the first clinical milestone and developed more milestones before death. Gender, age at disease onset and the time to reach any of the seven milestones of disease advancement were shown to predict disease duration. Apart from being admitted to residential care in MSA, no single milestone was found to influence survival, which may suggest that the intrinsic clinical subgroups of PSP and MSA have more prognostic significance and independently influence disease duration.

The mean disease duration in both PSP (8.0 ± 4.1 years) and MSA (7.9 ± 2.8) in our study was similar to previous clinical studies (Maher and Lees, 1986; Golbe et al., 1988; Ben-Shlomo et al., 1997; Testa et al., 2001; Watanabe et al., 2002; Golbe and Ohman-Strickland, 2007). Patients with PSP reached the majority of the clinical milestones after a significantly shorter interval from disease onset than in MSA, with only urinary catheterization tending to occur
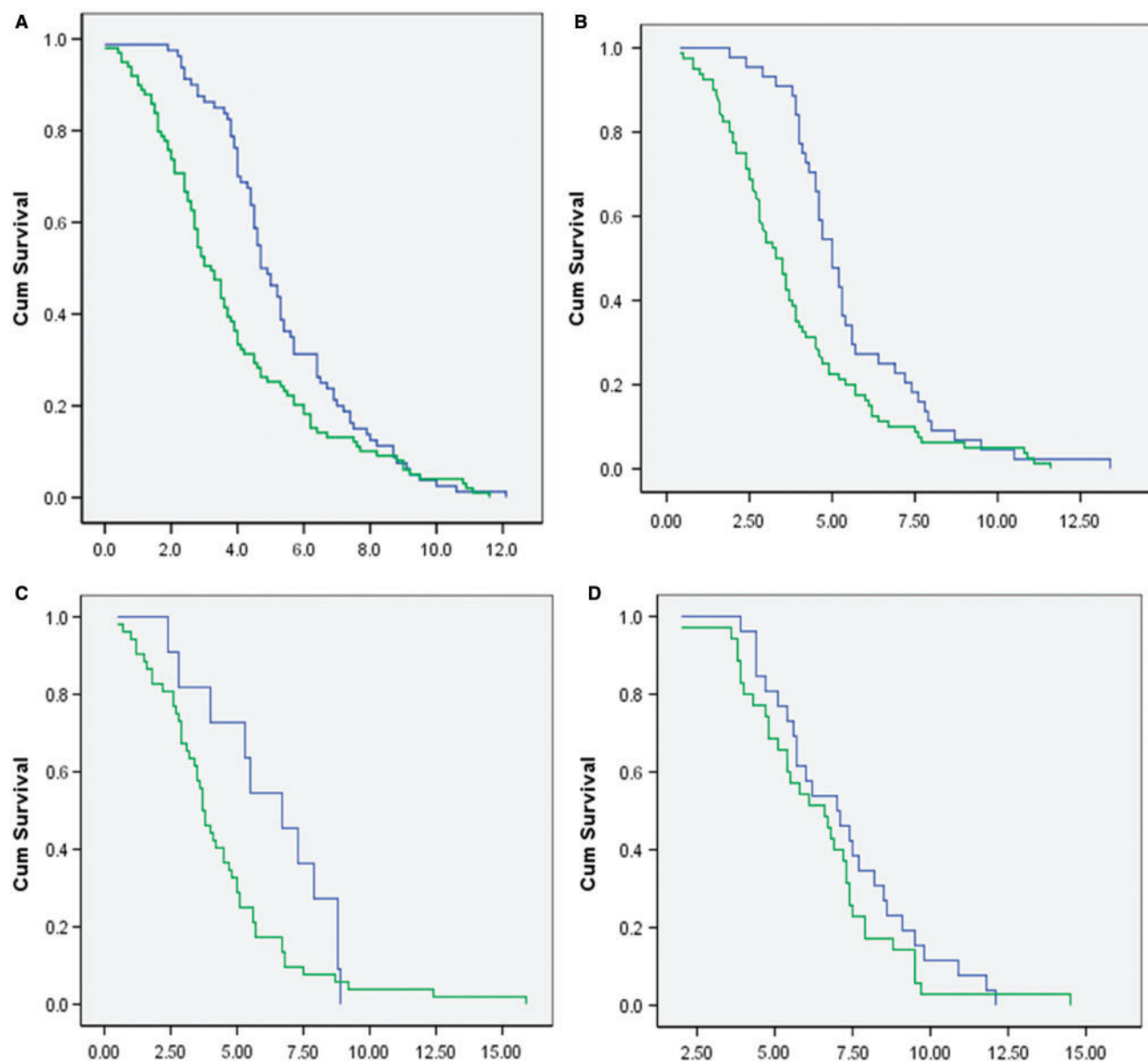
Fig. 3 Comparison between PSP and MSA of interval from disease onset to reaching clinical milestones. **(A)** Interval in years from disease onset to the first clinical milestone reached. Log Rank (Mantel-Cox), df = 1, *P* = 0.004. PSP, green dotted line; MSA, blue dotted line. **(B)** Interval in years from disease onset to developing frequent falls. Log Rank (Mantel-Cox), df = 1, *P* = 0.003. PSP, green dotted line, MSA, blue dotted line. **(C)** Interval in years from disease onset to developing significant cognitive impairment. Log Rank (Mantel-Cox), df = 1, *P* = 0.07. PSP, green dotted line MSA, blue dotted line. **(D)** Interval in years from disease onset to developing significant dysphagia. Log Rank (Mantel-Cox), df = 1, *P* = 0.29. PSP, green dotted line; MSA, blue dotted line. **(E)** Interval in years from disease onset to developing wheelchair dependence. Log Rank (Mantel-Cox), df = 1, *P* = 0.95. PSP, green dotted line; MSA, blue dotted line. **(F)** Interval in years from disease onset to developing unintelligible speech. Log Rank (Mantel-Cox), df = 1, *P* = 0.28. PSP, green dotted line; MSA, blue dotted line. **(G)** Interval in years from disease onset to requiring urinary catheterization. Log Rank (Mantel-Cox), df = 1, *P* = 0.79. PSP, green dotted line; MSA, blue dotted line. **(H)** Interval in years from disease onset to requiring residential care. Log Rank (Mantel-Cox), df = 1, *P* = 0.23. PSP, green dotted line, MSA, blue dotted line.

earlier in the course of MSA. This suggests that although disease duration in these two conditions is similar, PSP is more debilitating. It also suggests that although the milestones are useful indicators of morbidity, their relationship to the actual causes of death is not straightforward. Our finding that patients with PSP have a longer duration of frequent falling (mean 3.8 years) and cognitive

impairment (mean 2.4 years) may be of particular relevance for families attempting to care for patients at home, and may explain why more patients with PSP required residential care after a shorter interval from disease onset, than those with MSA.

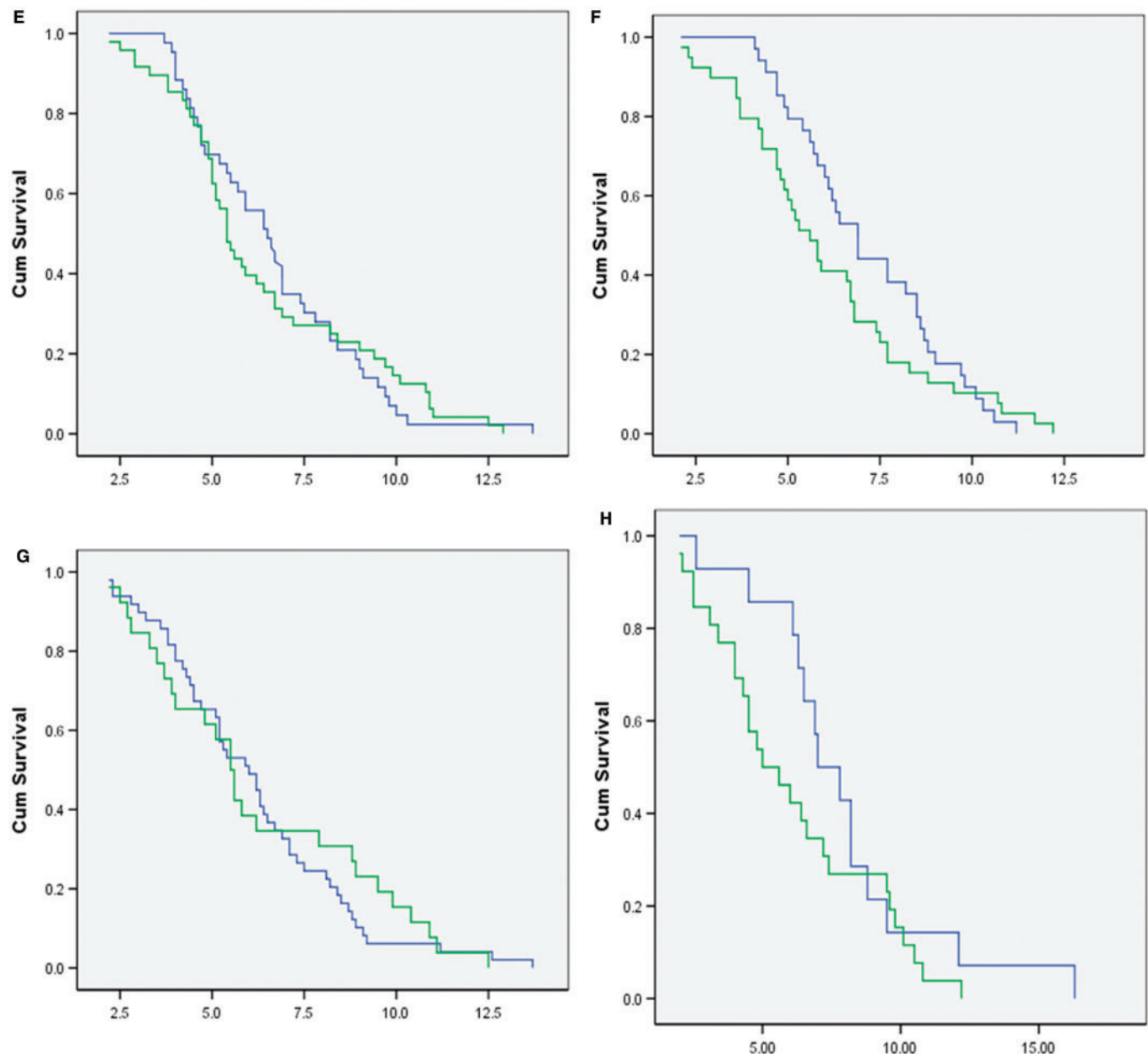Smaller studies of pathologically confirmed PSP cases have suggested that early falls and dementia

Fig. 3 Continued.

(Papapetropoulos *et al.*, 2005), and early dysphagia and urinary incontinence (Litvan *et al.*, 1996b), are poor prognostic indicators. Using a Cox multiple stepwise regression analysis we show that male gender, a short interval from disease onset to any clinical milestones and older age of onset are also independently associated with shorter disease duration in PSP. Another study of clinical cases of PSP found that older age of disease onset, but not gender, was associated with a significantly higher relative mortality (Golbe *et al.*, 1988; Nath *et al.*, 2003). The most significant predictor of a decreased survival in PSP is the RS clinical subtype (HR = 2.37, 95% CI = 1.21–4.64). This recently defined subgroup of PSP has been shown to have

more severe tau pathology (Williams *et al.*, 2007), and a subtly different insoluble tau-isoform composition than PSP-P (Williams *et al.*, 2005).

No studies have assessed the clinical progression of the proposed PSP subtypes, although early falls, a diagnostic feature of RS, has been associated with a shorter survival (Williams *et al.*, 2006). In our study, RS patients had a similar age at disease onset but more rapid disease progression than patients with PSP-P. This is seen not only in the Kaplan-Meier survival curves, which demonstrate a shorter disease course in RS, but also in the total number of other milestones reached. Patients with RS developed frequent falls and became wheelchair dependant
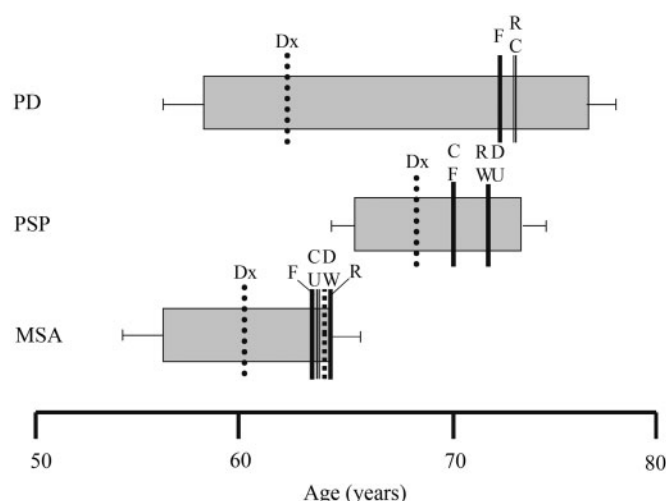
Fig. 4 Milestones of disease advancement and total disease course. The grey rectangles represent disease duration, commencing with the time point of first symptoms. The vertical lines denote time of clinical diagnosis of a parkinsonian or cerebellar syndrome (Dx) and time of documentation of milestones of disease advancement (Residential care, R; Cognitive disability, C; Dysarthria/dysphagia, D; Frequent falls, F; Wheelchair dependant, W; Urinary catheter, U). Error bars for standard error of the mean.

earlier than those with PSP-P. There was also a trend for patients with RS to reach non-ambulation-related milestones (severe dysphagia, unintelligible speech, significant cognitive impairment, urinary catheterization) and to require residential care at an earlier stage.

In MSA, we identified a number of clinical features that were associated with a poor prognosis: female gender, an older age of onset, a short interval from disease onset to the development of the first clinical milestone and not being admitted to residential care were independent factors predicting shorter disease duration until death. Older age of MSA onset was associated with increased risk of death and wheelchair dependence in a study by Watanabe and colleagues, although gender did not affect prognosis (Watanabe *et al.*, 2002). Klockgether and colleagues found older age of disease onset was associated with decreased survival. Although the risk of wheelchair dependence was greater in females, there was no significant male–female survival difference (Klockgether *et al.*, 1998). The apparent beneficial effect on survival from admission to a nursing home is interesting, as this is not seen in PSP. Milestones like severe dysphagia are seen in a similar proportion of patients with PSP, which may suggest that in MSA more than PSP, clinical aspects other than nutritional safety may benefit from nursing home care. This may include management of urinary tract infections, which were shown to be a cause of death in 5/21 cases in MSA (Papapetropoulos *et al.*, 2007).

The most important early clinical prognostic feature regarding survival we identified in MSA was that of early autonomic dysfunction (HR = 6.0, 95% CI = 3.1–11.7).

In previous studies in non-pathologically confirmed cases, which compared outcomes according to prominent symptom types, MSA-P patients have been shown to have more rapid functional deterioration than MSA-C patients (Schulz *et al.*, 1994; Watanabe *et al.*, 2002). This finding was not replicated in a study of 49 pathologically proven MSA cases, with Tada and colleagues instead describing a poor prognosis in patients presenting with autonomic dysfunction within 2.5 years of the onset of MSA symptoms (Tada *et al.*, 2007). Patients with concomitant motor and autonomic dysfunction within 3 years of symptom onset had a shorter survival duration, in addition to becoming wheelchair dependant and bed-ridden at an earlier stage than those who developed these symptoms after 3 years from symptom onset (Watanabe *et al.*, 2002).

Patients with MSA with autonomic dysfunction had shorter disease duration but similar age of disease onset. The higher proportion of males in the autonomic dysfunction group almost certainly reflects the presence of erectile failure as an early symptom in contrast to the lack of documentation of secondary anorgasmia as a symptom of sexual dysfunction in women, a finding noted in previous studies (Wenning *et al.*, 1994a). Therefore, we feel that these data do not necessarily support an assumption of early autonomic dysfunction being more common in male patients with MSA as compared with females. Although we did not find differences between MSA subgroups when analysing the interval from disease onset to the development of other clinical milestones, we show that when patients with early autonomic dysfunction develop frequent falling, or wheelchair dependence, or severe dysphagia, or require residential care, there is a shorter interval from this point to death. These findings may suggest an accelerated later stage of disease progression in this patient subgroup.

The response to levodopa did not influence survival in MSA or PSP. A higher proportion of patients with MSA (62.9%) than PSP (33.7%) showed improvement when levodopa was started, although there was little difference in frequency of sustained levodopa response. These response rates in MSA are similar to previous series with pathological confirmation, which show that between 30% and 70% benefit from levodopa (Wenning *et al.*, 2004). Data on levodopa response in PSP is limited, with response rates of between 30% and 50% described in series without pathological confirmation, of which many show only mild and short-lived improvement (Burn and Warren, 2005). Even if patients with PSP or MSA continue to respond to levodopa, the degree of the response is likely to be modest and insufficient to alter the overall survival. This contrasts with PD, in which a much higher proportion of patients respond to levodopa, with the majority of recent studies suggesting that levodopa reduces mortality in PD at least to a modest degree (Katzenschlager and Lees, 2002).

Pathological ascertainment is the great strength of our study, but there are limits to the accuracy of reconstruction

of clinical histories from medical records that may be compiled by professionals with various levels of clinical expertise, and without methodological uniformity. The milestones were generally identified with confidence, but it was harder to be sure that a particular clinical feature never occurred. Less frequent clinical follow-up may have delayed the first recording of a milestone in some cases.

The selection bias of a brain bank post-mortem series may also account for differences in our findings compared with previous clinical studies. Potential biases identified in previous autopsy studies include an over-representation of demographically less-typical and diagnostically more challenging cases, thereby leading to elevated rates of misdiagnosis and excessively pessimistic survival data (Maraganore *et al.*, 1999). Because the QSBB specializes in parkinsonian disorders, we may be more likely to have a disproportionate amount of cases with MSA-P phenotypes in our analysis, potentially reducing the ability to generalize our findings to cases of MSA with more prominent early cerebellar features. Similarly, it is possible that our cohort of PSP cases may be more likely to represent a parkinsonian phenotype, rather than PSP cases with prominent behavioural or cognitive presentations.

Common clinical experience and past research show that, in comparison to PD, both PSP and MSA are malign disorders. Some of the reasons for this are apparent in Fig. 4. In PSP, cognitive and gait milestones were reached relatively early and patients tended to survive with substantial disability for several years. Mean age of onset of MSA was younger than both PD and PSP, but the time between first symptoms and death was similar to PSP and much shorter than PD. In MSA, many disability milestones accumulated over a short period of time, with deleterious effect. This perspective of the whole disease course should help clinicians to anticipate patterns of disease progression in the palliative management of patients with PSP and MSA. Our findings may also furnish historical control data for future interventional studies.

Acknowledgements

References

Ben-Shlomo Y, Wenning GK, Tison F, Quinn NP. Survival of patients with pathologically proven multiple system atrophy: a meta-analysis. Neurology 1997; 48: 384–93.

Burn DJ, Warren NM. Toward future therapies in progressive supranuclear palsy. Mov Disord 2005; 20 (Suppl 12): S92–8.

Daniel SE, de Bruin VM, Lees AJ. The clinical and pathological spectrum of Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy): a reappraisal. Brain 1995; 118 (Pt 3): 759–70.

DSM-IV. Diagnostic and statistical manual of mental disorders. Washington: American Psychiatric Association; 1995.

Fearnley JM, Lees AJ. Striatonigral degeneration. A clinicopathological study. Brain 1990; 113 (Pt 6): 1823–42.

Gibb GM, de Silva R, Revesz T, Lees AJ, Anderton BH, Hanger DP. Differential involvement and heterogeneous phosphorylation of tau isoforms in progressive supranuclear palsy. Brain Res Mol Brain Res 2004; 121: 95–101.

Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, et al. Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci 1999; 163: 94–8.

Golbe LI, Davis PH, Schoenberg BS, Duvoisin RC. Prevalence and natural history of progressive supranuclear palsy. Neurology 1988; 38: 1031–4.

Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. Brain 2007; 130: 1552–65.

Hauw JJ, Daniel SE, Dickson D, Horoupian DS, Jellinger K, Lantos PL, et al. Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology 1994; 44: 2015–9.

Hughes AJ, Colosimo C, Kleedorfer B, Daniel SE, Lees AJ. The dopaminergic response in multiple system atrophy. J Neurol Neurosurg Psychiatry 1992; 55: 1009–13.

Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain 2002; 125: 861–70.

Hughes AJ, Daniel SE, Lees AJ. Idiopathic Parkinson's disease combined with multiple system atrophy. A clinicopathological report. Mov Disord 1991; 6: 342–6.

Katzenschlager R, Lees AJ. Treatment of Parkinson's disease: levodopa as the first choice. J Neurol 2002; 249 (Suppl 2): II19–24.

Kempster PA, Williams DR, Selikhova M, Holton J, Revesz T, Lees AJ. Patterns of levodopa response in Parkinson's disease: a clinico-pathological study. Brain 2007 Aug;130(Pt 8):2123–8. Epub 2007 Jun 24.

Klockgether T, Ludtke R, Kramer B, Abele M, Burk K, Schols L, et al. The natural history of degenerative ataxia: a retrospective study in 466 patients. Brain 1998; 121 (Pt 4): 589–600.

Litvan I, Hauw JJ, Bartko JJ, Lantos PL, Daniel SE, Horoupian DS, et al. Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. J Neuropathol Exp Neurol 1996a; 55: 97–105.

Litvan I, Mangone CA, McKee A, Verny M, Parsa A, Jellinger K, et al. Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopatho-logical study. J Neurol Neurosurg Psychiatry 1996b; 60: 615–20.

Lowe JLG, Leigh PN. Greenfield's neuropathology. In: Graham DI, Lantos PL, editors. Disorders of movement and system degeneration. 6 edn., London: Arnold; 1997. p. 297–300.

Maher ER, Lees AJ. The clinical features and natural history of the Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology 1986; 36: 1005–8.

Maraganore DM, Anderson DW, Bower JH, McDonnell SK, Rocca WA. Autopsy patterns for Parkinson's disease and related disorders in Olmsted County, Minnesota. Neurology 1999; 53: 1342–4.

Morris HR, Gibb G, Katzenschlager R, Wood NW, Hanger DP, Strand C, et al. Pathological, clinical and genetic heterogeneity in progressive supranuclear palsy. Brain 2002; 125: 969–75.

Nath U, Ben-Shlomo Y, Thomson RG, Lees AJ, Burn DJ. Clinical features and natural history of progressive supranuclear palsy: a clinical cohort study. Neurology 2003; 60: 910–6.

Office of National Statistics. http://www.statistics.gov.uk/CCI/nugget.asp?ID=168&Pos=1&ColRank=1&Rank=374: Office for National Statistics, 2007. Accessed January 2008.

Ozawa T, Paviour D, Quinn NP, Josephs KA, Sangha H, Kilford L, et al. The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopatho-logical correlations. Brain 2004; 127: 2657–71.

Papapetropoulos S, Gonzalez J, Mash DC. Natural history of progressive supranuclear palsy: a clinicopathologic study from a population of brain donors. Eur Neurol 2005; 54: 1–9.

Papapetropoulos S, Tuchman A, Laufer D, Papatsoris AG, Papapetropoulos N, Mash DC. Causes of death in multiple system atrophy. J Neurol Neurosurg Psychiatry 2007; 78: 327–9.

Papp MI, Kahn JE, Lantos PL. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). J Neurol Sci 1989; 94: 79–100.

Schrag A, Ben-Shlomo Y, Quinn NP. Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. Lancet 1999; 354: 1771–5.

Schulz JB, Klockgether T, Petersen D, Jauch M, Muller-Schauenburg W, Spieker S, et al. Multiple system atrophy: natural history, MRI morphology, and dopamine receptor imaging with 123IBZM-SPECT. J Neurol Neurosurg Psychiatry 1994; 57: 1047–56.

Tada M, Onodera O, Tada M, Ozawa T, Piao YS, Kakita A, et al. Early development of autonomic dysfunction may predict poor prognosis in patients with multiple system atrophy. Arch Neurol 2007; 64: 256–60.

Testa D, Monza D, Ferrarini M, Soliveri P, Girotti F, Filippini G. Comparison of natural histories of progressive supranuclear palsy and multiple system atrophy. Neurol Sci 2001; 22: 247–51.

Watanabe H, Saito Y, Terao S, Ando T, Kachi T, Mukai E, et al. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain 2002; 125: 1070–83.

Wenning GK, Ben-Shlomo Y, Hughes A, Daniel SE, Lees A, Quinn NP. What clinical features are most useful to distinguish definite multiple system atrophy from Parkinson's disease? J Neurol Neurosurg Psychiatry 2000; 68: 434–40.

Wenning GK, Ben-Shlomo Y, Magalhaes M, Daniel SE, Quinn NP. Clinicopathological study of 35 cases of multiple system atrophy. J Neurol Neurosurg Psychiatry 1995; 58: 160–6.

Wenning GK, Ben Shlomo Y, Magalhaes M, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. Brain 1994a; 117 (Pt 4): 835–45.

Wenning GK, Quinn N, Magalhaes M, Mathias C, Daniel SE. 'Minimal change' multiple system atrophy. Mov Disord 1994b; 9: 161–6.

Wenning GK, Colosimo C, Geser F, Poewe W. Multiple system atrophy. Lancet Neurol 2004; 3: 93–103.

Wenning GK, Tison F, Ben Shlomo Y, Daniel SE, Quinn NP. Multiple system atrophy: a review of 203 pathologically proven cases. Mov Disord 1997; 12: 133–47.

Williams DR, de Silva R, Paviour DC, Pittman A, Watt HC, Kilford L, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain 2005; 128: 1247–58.

Williams DR, Holton JL, Strand C, Pittman A, de Silva R, Lees AJ, et al. Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson's syndrome. Brain 2007; 130: 1566–76.

Williams DR, Watt HC, Lees AJ. Predictors of falls and fractures in bradykinetic rigid syndromes: a retrospective study. J Neurol Neurosurg Psychiatry 2006; 77: 468–73.