

Cognitive impairment in patients with multiple system atrophy and progressive supranuclear palsy

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This article reports the severity and profile of neuropsychological impairment on a prevalent cohort of patients with a clinical diagnosis of either multiple system atrophy ($n=372$) or progressive supranuclear palsy ($n=311$) from the Neuroprotection and Natural History in Parkinson Plus Syndromes cohort. The Dementia Rating Scale and Frontal Assessment Battery were used to assess global cognition and executive dysfunction. For the Dementia Rating Scale impairment was observed in ~57% of the progressive supranuclear palsy group and 20% of the multiple system atrophy group. In the former, impairment in a single cognitive domain was observed in 40%, with the same number showing impairment in multiple domains, while in the latter the figures were 28.6 and 13.5%, respectively. On the Frontal Assessment Battery, impairment was observed in 62.0% of patients with progressive supranuclear palsy and 31.8% of those with multiple system atrophy. Although the progressive supranuclear palsy group performed worse overall, the cognitive profiles of the two groups on the Dementia Rating Scale subscales were identical, with the main impairment of the Initiation and Perseveration subscale. The impaired patients in the two groups were largely indistinguishable, qualitatively and quantitatively. Impairment was associated with greater age and clinical disability in both groups and was evident even in the early stages (22% in multiple system atrophy and 50% in progressive supranuclear palsy). Where a pathological diagnosis was available, the original clinical diagnosis was confirmed in the majority of cases, including those with significant cognitive impairment. The rate of impairment in those with a confirmed pathological diagnosis was comparable to that of the sample as a whole. These results demonstrate, in the largest prospectively recruited cohort of

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patients with progressive supranuclear palsy and multiple system atrophy studied to date, the existence of a cognitive profile similar to that previously reported in idiopathic Parkinson's disease. The results indicate a high level of cognitive impairment associated with progressive supranuclear palsy, but also point to comparable dysfunction in a substantial proportion of the patients with multiple system atrophy. Significant cognitive impairment appears consistent with a diagnosis of multiple system atrophy, even early in the disease, with important implications for diagnosis, research and management.

Keywords: multiple system atrophy; progressive supranuclear palsy; natural history; cognitive impairment; outcome

Abbreviations: CGI = Clinician Global Impression; DRS = Mattis Dementia Rating Scale; ES = effect size; FAB = Frontal Assessment Battery; MMSE = Mini-Mental State Examination; NNIPPS = Neuroprotection and Natural History in Parkinson Plus Syndromes

Introduction

Early and accurate differentiation between parkinsonian syndromes is essential for both effective clinical management and research. Symptom profile and progression remain central to clinical diagnosis in the absence of reliable and/or widely available ante-mortem biomarkers. Consensus-based diagnostic criteria for progressive supranuclear palsy (Litvan *et al.*, 1996) and multiple system atrophy (Gilman *et al.*, 1999, 2008) have only been validated retrospectively. While retrospective case record studies of confirmed cases have provided useful information about clinical features and natural history, they do not offer the same quality of evidence as prospective studies. However, to date, such studies have tended to be limited in size and typically lack pathological confirmation of diagnosis. As a result, understanding of the natural history, clinical heterogeneity, genetics, pathophysiology and pathology has remained limited.

Early studies of cognitive function in progressive supranuclear palsy (Maher *et al.*, 1985; Pillon *et al.*, 1986; Dubois *et al.*, 1988; Litvan *et al.*, 1989; Milberg and Albert, 1989) described a profile similar to that seen in Parkinson's disease, although often more severe. Prominent deficits are described on tests of attention and executive function, with verbal fluency being particularly severely affected, as well as deficits in both verbal and non-verbal memory with a relative preservation of recognition. Subsequent studies have confirmed these early reports (Testa *et al.*, 1993; Robbins *et al.*, 1994; Esmonde *et al.*, 1996; Leiguarda *et al.*, 1997; Soliveri *et al.*, 2000; Lange *et al.*, 2003; Bak *et al.*, 2005a, 2006; Paviour *et al.*, 2005; Cotelli *et al.*, 2006; Krishnan *et al.*, 2006; Kaat *et al.*, 2007; Borroni *et al.*, 2008). In multiple system atrophy, qualitatively similar but less severe cognitive impairment is described (Sullivan *et al.*, 1991; Robbins *et al.*, 1992, 1994; Testa *et al.*, 1993, 2001; Meco *et al.*, 1996; Leiguarda *et al.*, 1997; Soliveri *et al.*, 2000; Berent *et al.*, 2002; Lange *et al.*, 2003; Bak *et al.*, 2005b, 2006; Paviour *et al.*, 2005; Burk *et al.*, 2006; Krishnan *et al.*, 2006; Kawai *et al.*, 2008).

Although evident in both progressive supranuclear palsy and multiple system atrophy, cognitive impairment is not a primary diagnostic criterion for either condition. It is currently viewed as a supportive feature in the diagnosis of progressive supranuclear palsy (Litvan *et al.*, 1996), but it has also been suggested that the presence of moderate to severe dementia early in the disease is

cause for caution in making the clinical diagnosis (Josephs and Dickson, 2003). In multiple system atrophy, the presence of significant cognitive decline is an exclusion feature by current consensus criteria (Litvan *et al.*, 1996; Gilman *et al.*, 1999, 2008).

Estimating dementia prevalence in progressive supranuclear palsy is hampered by a lack of large-scale prospective studies and frequent failure to report on cognition. Recent estimates range from 10% (Josephs and Dickson, 2003) to 52% (O'Sullivan *et al.*, 2008). Current consensus criteria explicitly rule out a diagnosis of multiple system atrophy if significant cognitive impairment is present, particularly at onset. Perhaps as a result, some large-scale case series have ignored cognition (Wenning *et al.*, 1994; Watanabe *et al.*, 2002). Nevertheless, dementia can occur in multiple system atrophy with estimates reported in the range of 14–16% (Wenning *et al.*, 2000; O'Sullivan *et al.*, 2008).

A fuller understanding of cognitive function in multiple system atrophy and progressive supranuclear palsy needs large-scale prospective studies with pathological confirmation of diagnosis where possible. In recent years, a number of study groups and consortia have been established (Vanacore *et al.*, 2001; Geser *et al.*, 2005, 2006; Gilman *et al.*, 2005) offering the opportunity to collect large samples of patients using standardized criteria, and applying a wide range of longitudinal assessment measures and analytical methods. This was achieved in the Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) study, a randomized, multi-centre, double blind, placebo controlled, stratified group study of the efficacy and safety of riluzole (up to 200 mg/day) in patients with multiple system atrophy and progressive supranuclear palsy (Bensimon *et al.*, 2009). The study included the collection of detailed clinical data over a period of 3 years in 760 patients, together with repeat neuroradiological, neuropsychological and neurobehavioural assessment and genetic analysis. Post-mortem examination was available in ~20% of cases and validated the accuracy of the NNIPPS diagnostic criteria. The present report focuses on the initial baseline (pre-randomization) neuropsychological assessment. This is the largest cohort of progressive supranuclear palsy and multiple system atrophy subjects yet evaluated prospectively in accordance with high standards of quality control and data audit, and thus provides a benchmark for the study of cognitive function in the two diseases.

Materials and methods

Sample

Selection, inclusion and exclusion criteria

A total of 760 patients were recruited from April 2000 to July 2002 (progressive supranuclear palsy, $n=362$; multiple system atrophy, $n=398$) from 44 specialist movement disorder services in the UK, France and Germany. Full details of the NNIPPS study including the NNIPPS diagnostic criteria that served as eligibility criteria for the present study are found elsewhere (Bensimon *et al.*, 2009) and in the Supplementary material. All patients met the defined criteria on entry to the study. No distinction was made between 'possible' or 'probable' diagnosis. Of specific relevance to the present report, multiple system atrophy patients with 'severe' dementia', operationalized as a Mini-Mental State Examination (MMSE) score <20 , were not included in the study.

Assessment

Before randomization all participants underwent a detailed series of clinical investigations and assessments. The MMSE (Folstein *et al.*, 1975) and the Frontal Assessment Battery (FAB) (Dubois *et al.*, 2000) were completed together with the Mattis Dementia Rating Scale (DRS) (Mattis, 1988). The DRS provides a more comprehensive assessment of cognitive function than the MMSE and FAB, with a wider range of scores possible (maximum score 144), plus separate indices of memory (visual, verbal and total), attention (visual, verbal and total), response initiation and perseveration (verbal, motor and total), construction and conceptualization. Where $>10\%$ of the data were missing the case was excluded from the analysis. Where missing data accounted for no more than 10% of the total possible score, the total and subscale scores were conservatively estimated by substituting the maximum score on the missing items. Cut-off scores were derived from normative data from 2058 individuals aged 58–105 years that took part in the Mayo Older American Normative Study (MOANS) (Lucas *et al.*, 1998) using the age ranges relevant to the present sample of patients. Impairment was defined both at a 5% level [DRS total score ≤ 125 , ~ 1.6 standard deviations (SD) below the population mean assuming a normal distribution], and stricter 1% level (DRS total score ≤ 119 , ~ 2.3 SD below the mean). Age-scaled scores (mean = 10, SD = 3) were also calculated for the DRS subscales using the same normative dataset. The 5% age-adjusted scaled score cut-off was ≤ 5 .

The FAB is designed to provide a brief assessment of the executive cognitive impairment associated with dysfunction to the frontostriatal system (Dubois *et al.*, 2000). It has six items, each rated on a 0–3 scale (maximum score 18). Performance on the test correlates well with other conventional tests of executive function (Lima *et al.*, 2008). The estimated FAB score was calculated only when the patient was able to complete three or more of the items (i.e. $\geq 50\%$ of the test). For the present study, impaired performance on the FAB was defined as a score of ≤ 14 based on published normative data (Appollonio *et al.*, 2005) and as used in other studies (Paviour *et al.*, 2005).

Patients were also assessed for clinical signs of cardiovascular dysautonomia, cerebellar, pyramidal, bulbar/pseudobulbar and ophthalmological impairment, and on the following clinical scales: Clinician Global Impression (CGI) of disease severity (Guy, 1976); the modified Hoehn and Yahr Scale (Fahn *et al.*, 1987); the Schwab and England Scale (Schwab and England, 1969); and a Short Motor Disability Scale

developed for the study (Bensimon *et al.*, 2009; see Supplementary material). Where an informant was available, depression was assessed using the Neuropsychiatric Inventory (Cummings *et al.*, 1994). A total score (maximum 12) was calculated from the product of depression frequency and severity. A score of ≥ 4 indicated significant depressive symptoms.

The protocol was filed in the open clinical trial registry (www.clinicaltrials.gov) with ID number NCT00211224.

Ethics

Prior to inclusion, patients gave their informed written consent to participate in the study. The NNIPPS protocol and amendments were reviewed and approved by the Comité de Protection des Personnes of Pitié-Salpêtrière Hospital (France), the UK Multicentre Research Ethics Committee (MREC) (UK), Ethikkommission of the University of Ulm (Germany) and by local Institutional Review Boards (Ethics Committees) where appropriate (UK, Germany). The trial was conducted according to International Standards of Good Clinical Practice (ICH guidelines and the Declaration of Helsinki).

Statistics

Because of the large sample size and the explorative nature of the evaluations, a conservative ($P < 0.01$) significance level was adopted for the between-group comparisons. No further adjustment was made for multiple comparisons, so differences close to this criterion level should be interpreted with caution. With large sample sizes it is often informative to consider effect sizes as well as P -values. To help compare the strength of observed group differences, the effect size measure partial eta squared is also reported with ANOVA/ANOCOVA results. This is the proportion of total variance (diagnosis effect plus error effect) that can be attributed to diagnosis. It is a measure of strength of association analogous to the R^2 statistic in linear regression. Binary logistic regression (Wald forward entry method) was used to investigate multivariate predictors of impairment.

Results

Sample size, demographic and clinical characteristics

Useable DRS data were available for 683 of the 760 participants (multiple system atrophy, $n=372$; progressive supranuclear palsy, $n=311$). MMSE (98.5%) and FAB (93.6%) data were available on almost all of these cases.

Table 1 shows the basic demographic and clinical characteristics of the patients included in this report. Patients in the progressive supranuclear palsy group were on average significantly older than those in the multiple system atrophy group [$t(681)=9.31$, $P < 0.001$] and had a trend towards fewer years of formal education [$t(677)=-1.76$, $P=0.016$]. Age and education were used as covariates in subsequent between group comparisons except for comparisons using adjusted scale scores. There were more males in both the multiple system atrophy and progressive supranuclear palsy groups but the proportions did not differ [$\chi^2(1)=0.75$,

Table 1 Demographic and clinical details of the multiple system atrophy and progressive supranuclear palsy groups

Measures	Multiple system atrophy (n=372)	Progressive supranuclear palsy (n=311)
Age (years)	61.71 (8.34)	67.75 (6.80)
Years of education	10.25 (3.55)	9.80 (3.16)
Gender (male) (%)	54.3%	57.2%
Disease duration (years)	4.55 (1.92)	3.90 (1.90)
Clinician Global Impression of disease severity ^a	3.0 (2.0–4.0)	3.0 (2.0–4.0)
Hoehn and Yahr ^a	3.0 (2.0–4.0)	3.0 (2.0–4.0)
Schwab and England	53.76 (24.25)	51.87 (23.20)
Short Motor Disability Scale	6.01 (3.68)	6.11 (3.40)
MMSE	27.60 (2.48)	25.51 (4.01)
FAB	14.23 (3.43)	11.33 (4.10)
Neuropsychiatric Inventory	2.09 (2.60)	2.17 (2.99)
Depression (frequency × severity)		
Neuropsychiatric Inventory Depression score ≥4 (%)	21.1	21.5
Cerebellar signs (%)	50.5	6.4
Dysautonomia (%)	56.7	12.5
Genitourinary signs (%)	87.1	50.0
Pyramidal signs (%)	53.7	47.9
Bulbar/pseudobulbar signs (%)	63.4	74.9
Ophthalmological signs (%)	19.1	99.9

Data are mean (SD) unless otherwise indicated.

^a Median and inter-quartile range.

$P=0.22$). The progressive supranuclear palsy group had significantly shorter disease duration [$t(679)=-4.48$, $P<0.001$]. However, the groups did not differ significantly in terms of CGI of disease severity ($z=-1.01$, $P=0.31$) or Hoehn and Yahr ratings ($z=-0.79$, $P=0.43$), or in terms of disability as assessed by the Schwab and England Scale [$t(678)=-1.04$, $P=0.30$] or Short Motor Disability Scale [$t(679)=0.36$, $P=0.72$]. MMSE [$t(671)=-8.29$, $P<0.001$] and FAB scores [$t(637)=-9.82$, $P<0.001$] were higher in the multiple system atrophy group. On clinical neurological examination, 76.5% of the patients with progressive supranuclear palsy and 37.9% of the patients with multiple system atrophy were considered cognitively impaired. The groups did not differ in terms of Neuropsychiatric Inventory depression score (multiple system atrophy, $n=327$; progressive supranuclear palsy, $n=279$) [$t(604)=0.35$, $P=0.72$] or in the proportions with significant depressive symptoms [$\chi^2(1)=0.02$, $P=0.90$].

Of the patients with progressive supranuclear palsy in the cohort, 85% were receiving levodopa at inclusion (mean daily dose 636 mg/day, range 50–2100 mg) and 84% of those with multiple system atrophy (mean daily dose 636 mg/day, range 50–2100 mg). The majority reported <25% improvement in their parkinsonian symptoms with treatment (Bensimon *et al.*, 2009).

Degree and profile of cognitive impairment

Table 2 shows the mean scores of the multiple system atrophy and progressive supranuclear palsy groups on the DRS. The progressive

supranuclear palsy group performed significantly worse on all of the global cognitive indices, even with age and education as covariates: DRS Total Score [$F(1,675)=96.13$, $P<0.001$, $ES=0.125$] and on each DRS subscales (in all cases $P<0.001$, $0.152>ES>0.043$).

Figure 1 shows the distribution of DRS total scores in the two patient groups. Of the progressive supranuclear palsy group, 57.2% scored below the 5% cut-off score with 40.5% scoring below the 1% cut-off. The corresponding figures for the multiple system atrophy group were 19.6 and 10.8%.

On the FAB, 71.8% of the progressive supranuclear palsy group scored below 15, while 62.0% scored below 14. For the multiple system atrophy group, the figures were 42.3 and 31.8%, respectively. On the MMSE, 33.6% of the progressive supranuclear palsy group scored below 25. A comparable figure for the multiple system atrophy group cannot be reported as patients with an MMSE of <20 were excluded from the study. However, 25.7% scored in the range 20–24.

Figure 2 shows the profile of age-scaled scores for the main DRS subscale totals. As for the raw scores shown in Table 2, the progressive supranuclear palsy group performed significantly worse ($P<0.001$) than the multiple system atrophy group for each scaled score. The progressive supranuclear palsy group showed mean lower levels of performance on all subscales with higher proportions of significant impairment. The most prevalent impairment (age scaled score ≤ 5) was for initiation and perseveration (73.0%), followed by memory (32.6%), conceptualization (23.9%), construction (20.4%) and attention (14.5%). Only one-fifth (20.4%) of patients with progressive supranuclear palsy showed no significant impairment on any cognitive domain and 39.4% showed impairment restricted to a single domain, while the remaining 40.2% showed impairments in two (16.4%) or more (23.8%) domains.

For the multiple system atrophy group, the mean scores lie close to the population average for each subscale, with the exception of initiation and perseveration where 36.8% of the sample showed impaired performance (age scaled score ≤ 5). For the remaining subscores, the percentages impaired were close to the average value from the normative data. The only exception was for memory where impairment was observed in 10.5%. Approximately two-thirds of the multiple system atrophy showed no significant impairment on any of the DRS subscales. Impairment in a single domain was found in 28.6%, while impairment in two or more domains was present in 13.5%.

Direct comparison between the two disease groups on the DRS subscales is complicated by the overall difference in levels of cognitive function. Figure 3 shows data only for those patients in each group with significant impairment at the 5% level (DRS total score ≤ 125). The progressive supranuclear palsy subgroup remain somewhat more impaired than the multiple system atrophy subgroup overall (DRS total mean: progressive supranuclear palsy = 107.34, $SD=17.99$; multiple system atrophy = 114.0, $SD=11.47$) [$F(1,239)=9.53$, $P<0.01$, $ES=0.038$]. In terms of the age-scaled subscale scores, the progressive supranuclear palsy subgroup were more impaired only on initiation and perseveration [$F(1,235)=14.15$, $P<0.001$, $ES=0.057$]. The subgroups did not

Table 2 Multiple system atrophy and progressive supranuclear palsy group DRS scores

Measures	Multiple system atrophy (n = 372)	Progressive supranuclear palsy (n = 311)
DRS total (max = 144)	131.88 (10.93)	117.83 (18.91)
DRS attention—total (max = 37)	35.44 (1.86)	33.80 (3.42)
DRS attention—verbal (max = 18)	16.91 (1.14)	16.19 (1.67)
DRS attention—visual (max = 19)	18.57 (1.24)	17.69 (2.35)
DRS initiation and perseveration—total (max = 37)	31.62 (5.37)	25.35 (6.80)
DRS initiation and perseveration—verbal (max = 30)	25.00 (4.92)	19.31 (6.01)
DRS initiation and preservation—motor (max = 7)	6.60 (0.95)	5.85 (1.62)
DRS construction (max = 6)	5.68 (1.01)	4.95 (1.80)
DRS conceptualization (max = 39)	35.96 (3.74)	32.58 (6.39)
DRS memory—total (max = 25)	23.20 (2.57)	21.22 (4.03)
DRS memory—orientation (max = 9)	8.48 (0.82)	7.79 (1.55)
DRS memory—sentence recall (max = 7)	6.01 (1.70)	5.17 (2.21)
DRS memory—verbal recognition (max = 5)	4.78 (0.62)	4.49 (1.01)
DRS memory—visual recognition (max = 4)	3.88 (0.42)	3.67 (0.80)

Data are mean (SD) unless otherwise indicated.
max = maximum scale or subscale score.

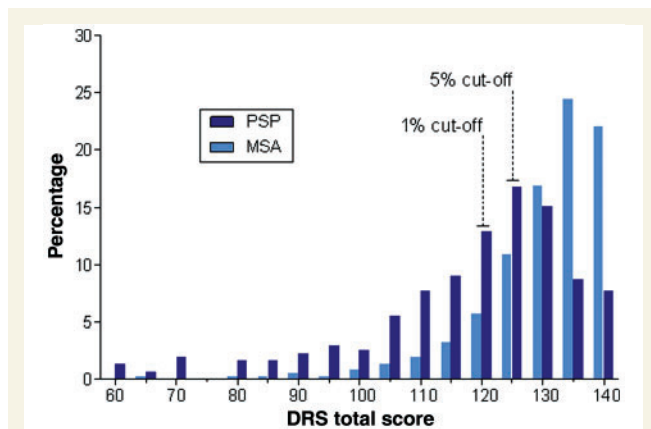


Figure 1 Frequency histogram of DRS total score for the multiple system atrophy (MSA) ($n = 372$) and progressive supranuclear palsy (PSP) ($n = 311$) groups. x -axis ticks marks shows bin centre (width 5) (cut-offs are approximate).

differ for attention [$F(1,239) = 6.05$, $P = 0.015$, $ES = 0.025$], construction [$F(1,227) = 2.29$, $P = 0.13$, $ES = 0.010$], conceptualization [$F(1,239) = 4.20$, $P = 0.04$, $ES = 0.017$] or memory [$F(1,232) = 0.73$, $P = 0.39$, $ES = 0.003$].

The subscale scores for initiation and perseveration and for memory reflect a number of separate DRS items. For both multiple system atrophy and progressive supranuclear palsy subgroups, the most marked deficits were observed in verbal initiation (fluency) and sentence recall.

Characteristics of cognitively impaired patients

Table 3 shows the clinical and demographic characteristics of multiple system atrophy and progressive supranuclear palsy patients with and without significant cognitive impairment. To maximize

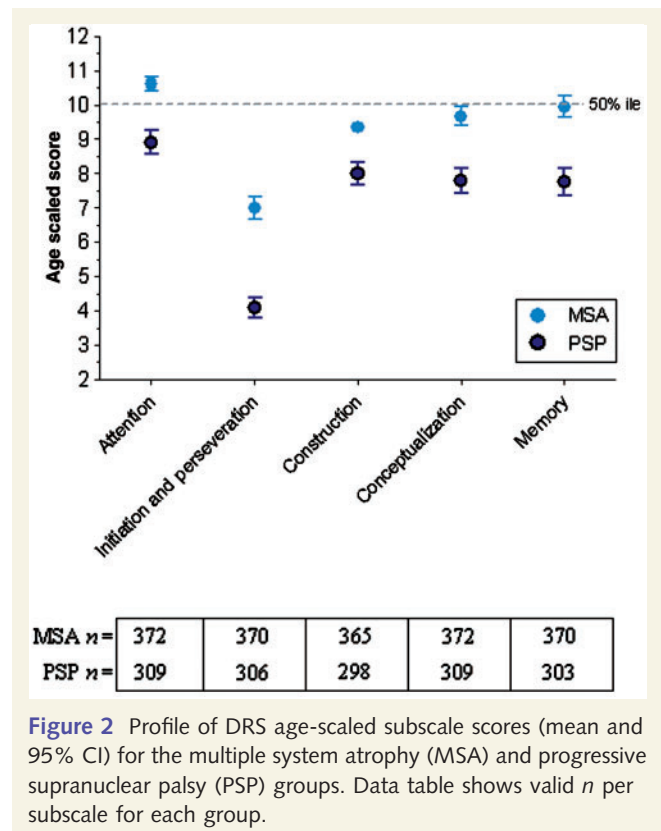


Figure 2 Profile of DRS age-scaled subscale scores (mean and 95% CI) for the multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) groups. Data table shows valid n per subscale for each group.

the separation of the subgroups, cognitive impairment was taken as a DRS total score of below the fifth percentile value (≤ 125). 'Unimpaired' cognition was defined by a DRS total score above the 25th percentile value (≥ 133). Patients with intermediate (borderline) function (DRS total score between 126 and 132) were not included in the analysis.

For both multiple system atrophy and progressive supranuclear palsy, patients with cognitive impairment were significantly older

than those without, and had more severe disease and disability as assessed by the CGI, Hoehn and Yahr Scale, Schwab and England and Short Motor Disability Scale (in all instances $P < 0.001$). In

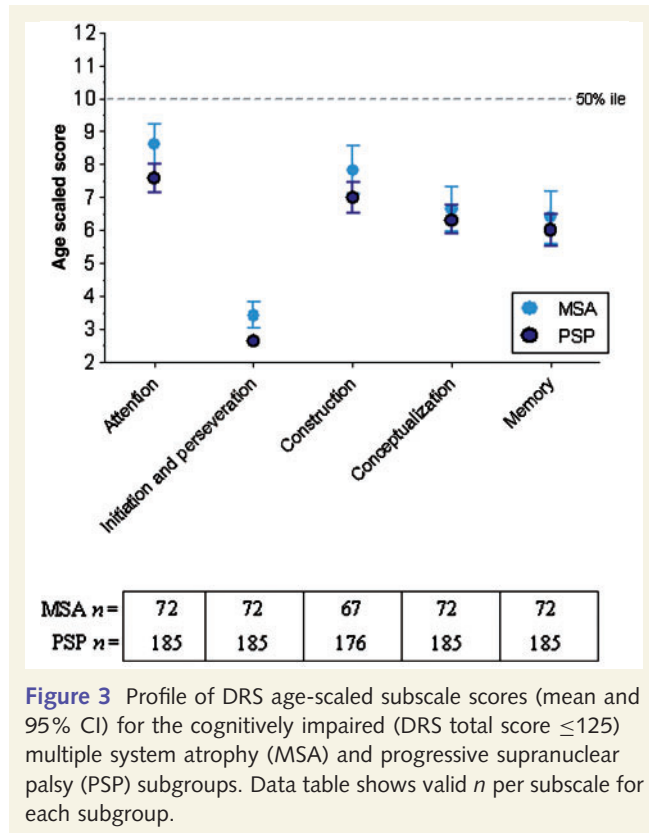


Figure 3 Profile of DRS age-scaled subscale scores (mean and 95% CI) for the cognitively impaired (DRS total score ≤ 125) multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) subgroups. Data table shows valid n per subscale for each subgroup.

multiple system atrophy [$F(1,284) = 31.92$, $P < 0.001$, $ES = 0.10$] but not progressive supranuclear palsy [$F(1,237) = 0.40$, $P = 0.53$, $ES < 0.001$] cognitive impairment was related to fewer years of formal education. Depressive symptoms were more severe in the unimpaired patients [$F(1,465) = 8.19$, $P = 0.004$, $ES = 0.017$], an effect present in both groups [$F(1,465) = 0.17$, $P = 0.69$, $ES < 0.001$].

In multiple system atrophy, impaired patients had longer mean disease duration than the unimpaired [$F(1,285) = 8.34$, $P < 0.01$, $ES = 0.03$], although across the sample as a whole total DRS score was only weakly associated with disease duration ($r = -0.16$, $P = 0.002$). Figure 4 shows the proportion of patients with cognitive impairment plotted against disease duration. While the rate of impairment remained relatively constant, there is some indication of an increased prevalence to almost 50% in the small number (7%) surviving with multiple system atrophy for ≥ 8 years. In progressive supranuclear palsy, there was no significant difference in mean duration between those with and without cognitive impairment [$F(1,238) = 0.095$, $P = 0.76$, $ES < 0.001$]. Figure 4 shows that the prevalence of cognitive impairment is high in the first few years but then tended to decline in those surviving longest. For the small number (16.7%) of patients with progressive supranuclear palsy, who had survived for ≥ 6 years, cognitive impairment appears to be a less typical feature of the clinical profile.

Disease duration and disease stage are only partially related, reflecting different rates of disease progression. We explored the prevalence of impairment in 4 subgroups: early mild disease (duration < 4 years, CGI-disease severity ≤ 2), late advanced disease (duration ≥ 4 years CGI-disease severity ≥ 3) and in early advanced disease and late mild disease, although the number in this latter subgroup were small (Table 4). In the patients with multiple

Table 3 Demographic and clinical measures in cognitively impaired (DRS ≤ 125) and unimpaired (DRS ≥ 133) multiple system atrophy and progressive supranuclear palsy patient groups

Measures	Multiple system atrophy		Progressive supranuclear palsy	
	Impaired (n = 73)	Unimpaired (n = 299)	Impaired (n = 185)	Unimpaired (n = 126)
Age (years)	65.07 (8.53)	60.57 (7.92)	68.90 (6.52)	64.61 (7.34)
Years of education	8.50 (3.46)	11.09 (3.34)	9.61 (3.40)	9.93 (2.51)
Gender (male) (%)	61.4	52.8	61.6	47.3
Disease duration (years)	4.99 (2.30)	4.24 (1.76)	3.91 (1.92)	3.83 (1.81)
Clinician Global Impression of disease severity ^a	4.0 (4.0–5.0)	3.0 (3.0–4.0)	4.0 (3.0–5.0)	3.0 (3.0–4.0)
Hoehn and Yahr ^a	4.0 (3.5–5)	3.0 (2.5–4.0)	4.0 (3.0–5.0)	3.0 (3.0–4.0)
Schwab and England	40.96 (21.68)	61.08 (22.50)	45.46 (21.11)	66.18 (21.98)
Short Motor Disability Scale	7.24 (3.58)	5.16 (3.38)	6.84 (3.59)	4.18 (2.70)
MMSE	23.78 (1.86)	28.34 (1.86)	22.96 (4.37)	27.71 (2.14)
FAB	9.48 (4.05)	15.22 (2.45)	8.70 (3.99)	13.84 (2.57)
Neuropsychiatric Inventory Depression (frequency \times severity)	1.79 (2.47)	2.52 (2.63)	1.54 (2.40)	2.51 (3.18)
Neuropsychiatric Inventory Depression score ≥ 4 (%)	15.6	30.4	18.0	23.8
Cerebellar signs (%)	50.7	49.2	5.4	7.9
Dysautonomia (%)	68.1	53.8	10.4	15.9
Genitourinary signs (%)	80.8	88.6	52.7	45.2
Pyramidal signs (%)	53.4	53.8	48.6	47.6
Bulbar/pseudobulbar signs (%)	69.9	61.8	70.5	80.2
Ophthalmological signs (%)	23.3	18.1	100	99.9

Data are mean (SD) unless otherwise indicated.

^a Median and inter-quartile range.

system atrophy, impairment was as prevalent in patients with early mild disease (22%) as in late advanced disease (24%). In progressive supranuclear palsy also, impairment was evident even in those with early mild disease (50%) with similar levels of impairment (61–63%) those with more advanced disease regardless of duration.

Binary logistic regression (Wald forward entry method) was used to investigate multivariate predictors of impairment in the multiple system atrophy and progressive supranuclear palsy groups in turn. Dichotomized variables examined were: gender (male/female), age (<65/≥65 years), education (<10/≥10 years), disease duration (<4/≥4 years), CGI (<3/≥3), Short Motor Disability Scale (<5/≥5), Neuropsychiatric Inventory depressive symptoms (<4/≥4) and the presence/absence of dysautonomia, cerebellar, genitourinary, pyramidal, bulbar/pseudo bulbar and ophthalmological signs. For the progressive supranuclear palsy group, cognitive impairment was predicted by greater motor disability [Wald=7.06, $P=0.008$, odds ratio (OR)=2.14, 95% confidence interval (CI) 1.22–3.75] and older age ($W=4.04$,

$P=0.04$, OR=1.75, CI 1.01–3.02), together with the absence of bulbar/pseudobulbar ($W=7.70$, $P=0.006$, OR=2.41, CI 1.30–4.48) and cardiovascular autonomic signs ($W=4.44$, $P=0.04$, OR=2.29, CI 1.06–4.94). In the multiple system atrophy group, cognitive impairment was predicted by greater motor disability ($W=9.26$, $P<0.001$, OR=3.58, CI 1.75–7.29), fewer than 10 years of education ($W=4.99$, $P=0.03$, OR=2.27, CI 1.10–4.65), male gender ($W=4.55$, $P=0.03$, OR=1.94, CI 1.05–3.56), the presence of cardiovascular dysautonomia ($W=8.60$, $P=0.003$, OR=2.64, CI 1.34–5.05) and the absence of genitourinary signs ($W=10.85$, $P=0.001$, OR=4.02, CI 1.67–9.60).

Cognitive impairment and histopathological diagnosis

Finally, we examined diagnostic accuracy in relation to cognitive status. A pathological diagnosis (conducted blind to clinical diagnosis or cognitive status) was available on 112 patients at the time of writing, 63 with a clinical diagnosis of progressive supranuclear palsy at the time of initial assessment and 49 with a clinical diagnosis of multiple system atrophy. Assessable DRS data were available for 51 of the progressive supranuclear palsy group and 44 of the multiple system atrophy group. Of those without DRS data, MMSE scores were available for nine of the patients with progressive supranuclear palsy and all of those with multiple system atrophy. For this analysis, impairment was defined as a DRS score of ≤125 or MMSE score ≤24. The MMSE score was used for tentative classification only when a DRS score was not available. Cognitive status was not assessed or was not assessable in three patients, all with a clinical diagnosis of progressive supranuclear palsy that was confirmed on pathological examination.

The majority (76.7%) of the progressive supranuclear palsy group coming to post-mortem were cognitively impaired at the time of the initial assessment, and diagnosis was confirmed in 89.1%. In four of the impaired patients, significant coincident Alzheimer pathology (Braak stage 4–5) was reported, although no patient received a primary diagnosis of Alzheimer's disease. Cases where an alternative diagnosis was made included cortico-basal degeneration, Lewy body disease and amyotrophic lateral sclerosis, plus one impaired patient with an initial clinical diagnosis of progressive supranuclear palsy received a final diagnosis of multiple system atrophy. Diagnostic accuracy was 85.7% in the

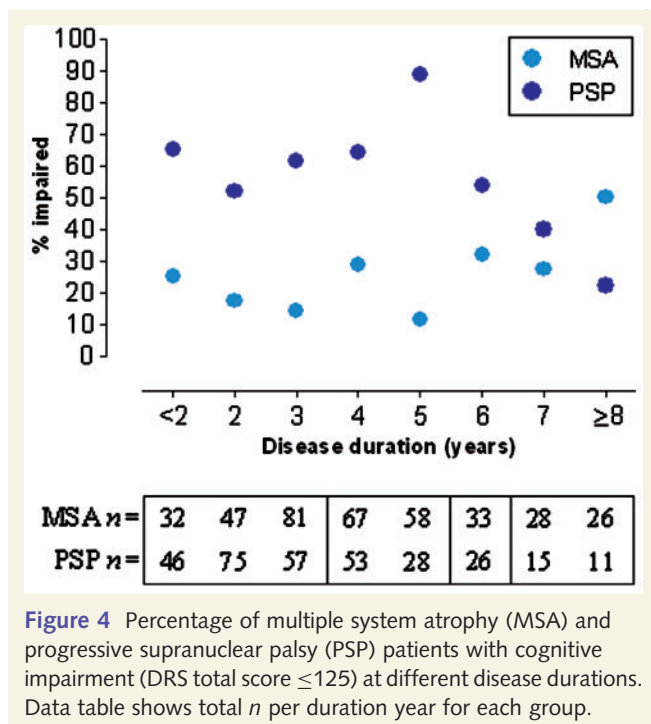


Figure 4 Percentage of multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) patients with cognitive impairment (DRS total score ≤125) at different disease durations. Data table shows total n per duration year for each group.

Table 4 Percentage of cognitively impaired (DRS ≤125) patients in multiple system atrophy and progressive supranuclear palsy groups according to Clinician Global Impression disease severity and disease duration at assessment

CGI of disease severity	Multiple system atrophy			Progressive supranuclear palsy		
	Disease duration			Disease duration		
	<4 years	≥4 years	Total	<4 years	≥4 years	Total
3–6	15% (137)	24% (197)	20% (334)	61% (138)	63% (123)	62% (261)
1–2	22% (23)	0 (15)	13% (38)	50% (40)	30% (10)	46% (50)
Total	16% (160)	23% (212)	20% (372)	58% (178)	61% (133)	59% (311)

Numbers in parentheses show the total number of patients in the cell regardless of impairment and the percentages are depicted outside the parentheses. CGI = Clinician Global Impression.

unimpaired group including one case with multiple system atrophy.

In the multiple system atrophy group, 22.9.0% were classified as impaired on initial assessment. Of these, the diagnosis was confirmed in 64.4% with a final diagnosis of progressive supranuclear palsy, Lewy body disease or amyotrophic lateral sclerosis in the remainder. In the unimpaired group, diagnosis of multiple system atrophy was confirmed in 94.6% of cases.

Based on the final pathological diagnosis, 43/54 (79.6%) of the confirmed patients with progressive supranuclear palsy were cognitively impaired at initial assessment and 8/44 (18.2%) of the confirmed patients with multiple system atrophy.

Discussion

The NNIPPS study offers a unique opportunity to study the degree of cognitive impairment and its profile in a very large sample of patients with a clinical, and in some cases pathological, diagnosis of multiple system atrophy or progressive supranuclear palsy. Not only were subjects prospectively recruited, but the study as a whole was performed to standards of good clinical practice for data quality. As expected, cognitive impairment was more evident in the progressive supranuclear palsy group. On the DRS, FAB and MMSE, mean scores were lower in progressive supranuclear palsy and the differences from multiple system atrophy were highly statistically significant. Thus, as already known, early cognitive impairment is common in progressive supranuclear palsy, although our results show further that significant cognitive impairment can be detected in multiple system atrophy on tests such as the DRS even in the early stages (~25% of patients within 2 year of diagnosis).

The profiles of cognitive impairment indicated by the distribution of DRS subscale scores largely support the findings of a previous smaller scale study (Bak *et al.*, 2005a) and the general pattern observed in studies using a range of different instruments. In both multiple system atrophy and progressive supranuclear palsy the salient impairment is on the DRS initiation and perseveration subscale, and particularly the verbal items. Verbal fluency makes the greatest contribution to this score, confirming previous reports of the tests value in detecting cognitive impairment in these patient groups (Maher *et al.*, 1985; Dubois *et al.*, 1988; Milberg and Albert, 1989; Soliveri *et al.*, 2000; Lange *et al.*, 2003; Krishnan *et al.*, 2006). Although differing in mean level of function, the profile observed in the multiple system atrophy and progressive supranuclear palsy groups appeared identical. The similarity is reinforced when comparing multiple system atrophy and progressive supranuclear palsy subgroups approximately matched for overall level of cognitive impairment. Although the progressive supranuclear palsy group still tended to be somewhat more impaired, there was little to distinguish them from the multiple system atrophy group, either qualitatively or quantitatively. The presence of cognitive impairment with a predominant deficit in verbal fluency appears to have little clinical significance in distinguishing between progressive supranuclear palsy and multiple system atrophy.

This evidence supports the idea of a core pattern of cognitive impairment in parkinsonian syndromes independent of underlying pathology, which probably reflects the direct consequence of both cortical and subcortical atrophy and their associated cortical pathophysiological changes. *In vivo* imaging studies indicate subcortical and frontal cortical atrophy in both progressive supranuclear palsy and multiple system atrophy with predominant parkinsonian motor symptoms and greater than that seen in Parkinson's disease (Paviour *et al.*, 2006). In that study, clinoradiological associations indicated that progressive supranuclear palsy cognitive impairment was associated with brain stem and frontal volumes (including cortex and basal ganglia), with strong association between frontal volume and verbal fluency scores. In the multiple system atrophy with predominant parkinsonian motor symptoms group, only mild executive impairment was seen and tended to be associated with posterior–inferior brain volume including specifically pons and cerebellar volumes. However, small sample size ($n=9$) and the absence of marked cognitive impairment makes it difficult to exclude the potential role of frontal pathology and pathophysiology as a cause of cognitive decline in multiple system atrophy, particularly later in the disease course. Even in the absence atrophy, changes in frontal metabolism may account for some of the executive impairment observed in multiple system atrophy (Kawai *et al.*, 2008).

As noted in the 'Introduction' section, there is little reliable or consistent evidence on the prevalence of cognitive impairment or dementia in progressive supranuclear palsy. From a recent report of 152 cases, of which 67 were assessable, 85% showed evidence of cognitive impairment although dementia criteria were not applied (Kaat *et al.*, 2007). The same study suggested that significant cognitive impairment can be an early and prominent sign in progressive supranuclear palsy, sometimes leading to an initial diagnosis of frontotemporal dementia before other classic progressive supranuclear palsy symptoms emerged (Kaat *et al.*, 2007). Similarly, 'cognitive problems' were reported as the initial presenting complaint in 15% of a prevalent sample of 187 cases (Nath *et al.*, 2001, 2003). In a sample of 90 pathologically confirmed progressive supranuclear palsy cases, dementia had been reported in 10% although 'memory/cognitive complaints' were reported in the notes of 32% (Josephs and Dickson, 2003). Another study using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV dementia criteria with a series of 110 cases, reported a prevalence of 52% with a mean duration of 4.2 years from disease onset (O'Sullivan *et al.*, 2008).

Evidence is even more sparse for multiple system atrophy. In a retrospective study of pathologically confirmed cases, dementia was identified in 15.7% of a sample of 38 multiple system atrophy cases (compared to 53% of a sample of Parkinson's disease cases) (Wenning *et al.*, 2000). In none of the multiple system atrophy cases was dementia reported within the first 5 years onset. In another case record study (O'Sullivan *et al.*, 2008), 14% of a sample of 83 pathologically confirmed cases of multiple system atrophy were identified as demented by DSM-IV criteria before death. Such retrospective data suggest that dementia can occur in patients with multiple system atrophy as a later feature of the disease. However, this picture may be partly a consequence of selection bias if multiple system atrophy was ruled out by early

cognitive impairment. A recent study in a group of 58 patients deliberately ignored the dementia exclusion criterion in making the clinical diagnosis (Kitayama *et al.*, 2009). Dementia was identified in 10 cases (17.2%), suggesting that dementia can co-exist with otherwise typical symptoms of multiple system atrophy.

Unlike dementia in Parkinson's disease where provisional criteria have recently been published (Emre *et al.*, 2007), we have no equivalent for the diagnosis of dementia in either multiple system atrophy or progressive supranuclear palsy. While DSM-IV (American Psychiatric Association, 2000) provides general criteria, applying these in patients with severe motor disability is problematic, particularly in attempting to judge the impact of the cognitive impairment on the individual's life. In the present study, we adopted operationalized criteria to define statistically significant cognitive impairment rather than trying to diagnose dementia. However, we anticipate that analysis of the longitudinal dataset will identify cases presenting with a progressive deterioration that might point more clearly to a dementia diagnosis.

The prevalence of impairment within the two groups differed depending on the test and criteria applied. On the DRS, whether adopting a 5% or stricter 1% cut-off, considerably more patients in both groups scored in these ranges than would be expected from the general population of the same age. In progressive supranuclear palsy, almost 60% scored below the fifth percentile value and 40% fell into the lowest range. Even in the multiple system atrophy group the figures were ~20 and 11%, respectively. These latter figures are noteworthy given that patients with an MMSE score of <20 were excluded from the study. This confirms the poor sensitivity of the MMSE in detecting cognitive impairment in parkinsonian syndromes and the superiority of scales such as the DRS (Bak *et al.*, 2005b).

If the cognitive profile in both multiple system atrophy and progressive supranuclear palsy is dominated by executive impairment, we would expect to detect even greater levels of impairment using tests that specifically measure such functions. Using norm-based cut-off for the FAB, 62% of the progressive supranuclear palsy group scored in the bottom 5% range and 32% of the patients with multiple system atrophy. Similarly, for the DRS initiation and perseveration subscale, 74% of the progressive supranuclear palsy group were impaired and 34% of those with multiple system atrophy. It is interesting that these latter figures are comparable to the proportions (76 and 38%) judged independently to have a 'cognitive syndrome' by the examining neurologist at inclusion (Bensimon *et al.*, 2009). This suggests that verbal spontaneity and speed of speech production may be the hallmark features used by clinicians to judge the presence of cognitive impairment in these groups.

An isolated impairment in executive function, although important, is not the same as the more generalized cognitive decline of the type expected in dementia. In the present study, multiple domain impairment was observed in ~40% of the progressive supranuclear palsy group and 14% of the multiple system atrophy group. Combining the various indicators, we can estimate that significant cognitive impairment was observed in 40–62% of patients with progressive supranuclear palsy and 11–32% of patients with multiple system atrophy, depending on the criteria and tests used. These ranges are compatible with estimates from the few

prospective and retrospective studies reviewed above. However, the size of the present sample provides the most reliable estimate to date, and allows a better evaluation of the clinical significance of the evidence. In particular, although only a minority of patients with multiple system atrophy were impaired, the figures still represented a significant proportion of the population being sampled, and may even be an underestimate.

The large sample size of the present study also offered opportunities to examine the natural history and clinical correlates of cognitive dysfunction in multiple system atrophy and progressive supranuclear palsy. In both conditions, cognitive impairment was related to more severe disease whether measured by CGI, Hoehn and Yahr stage or motor disability. Patients with multiple system atrophy showed evidence of cognitive impairment (20–30%) even in the early stages and mild of the disease (Fig. 4 and Table 4).

A similar picture emerges with the progressive supranuclear palsy group that we studied. There was evidence of high levels of cognitive impairment even in patients at the earliest stages of their disease and unrelated to disease duration, consistent with previous reports (Kaat *et al.*, 2007; Ghosh *et al.*, 2009). Previous reports have suggested that there are two distinct phenotypes of progressive supranuclear palsy with molecular differences in the tau isoforms: Richardson syndrome and progressive supranuclear palsy-parkinsonism (Williams *et al.*, 2005). Richardson syndrome is thought to represent classical progressive supranuclear palsy as first described, with early onset of postural instability and falls, supranuclear vertical gaze palsy and cognitive dysfunction. In the study of Williams and colleagues (2005), patients fitting this clinical profile comprised 54% of a sample of cases with the hallmark histopathological features of progressive supranuclear palsy. A second group of patients, also with confirmed progressive supranuclear palsy, presented with a different clinical profile: asymmetrical onset, tremor, a moderate initial therapeutic response to L-dopa and longer survival. Unlike progressive supranuclear palsy patients with Richardson syndrome, cognitive impairment in progressive supranuclear palsy-parkinsonism was a less prominent feature in the case records. Whether such phenotypes are represented in the current cohort is impossible to determine based on cross-sectional clinical data. Comparing patients with and without late cognitive impairment, the current cross-sectional data did not offer any strong support for the existence of clear phenotypic variants. However, fuller exploration of possible phenotypic variation will be possible with longitudinal analysis of the NNIPPS dataset.

Multiple system atrophy can also present with different clinical phenotypes, although there is no strong evidence that these represent different disease entities. The most common distinction is between patients presenting early with predominant parkinsonian motor symptoms (multiple system atrophy-P) and those with early predominant cerebellar symptoms (multiple system atrophy-C). With increasing disease duration both parkinsonian and cerebellar symptoms tend to emerge, although the presence of early parkinsonian symptoms has been associated with a more rapid functional decline (Watanabe *et al.*, 2002). Neuropsychological studies that have classified their patients as having multiple system atrophy-P or multiple system atrophy-C have described similar impairment in both subtypes (Sullivan *et al.*, 1991; Testa *et al.*, 1993; Soliveri

et al., 2000; Lange *et al.*, 2003; Burk *et al.*, 2006; Krishnan *et al.*, 2006; Kawai *et al.*, 2008), although all of the dementia patients in the study of Kitayame and colleagues (2009) had a multiple system atrophy-C type profile. To date, only one study has directly compared patients with multiple system atrophy-P and -C with 21 and 14 patients, respectively (Kawai *et al.*, 2008). That study described somewhat more severe and widespread impairment in the multiple system atrophy-P group associated with decreased frontal perfusion, despite similar disease duration. In the present study, the primary inclusion criteria required the presence of at least mild akinetic rigid parkinsonian symptoms which could have biased the sample towards multiple system atrophy-P. Half of the multiple system atrophy sample ($n = 184$) also had cerebellar symptoms at inclusion (Al-Chalabi *et al.*, 2009), although this failed to emerge as an independent predictor of cognitive impairment.

Another possible phenotypic variant in multiple system atrophy is whether autonomic dysfunction occurs early or later in the clinical profile. The clinicopathological study of O'Sullivan and colleagues (2008) indicated that early autonomic symptoms were associated with shorter time to death, although they found no association with the prevalence of dementia or time to onset. From our own data, cardiovascular dysautonomia emerged as an independent predictor of cognitive impairment.

A strength of the present study was the availability of a pathological diagnosis in a substantial proportion of the patients that had died ($n = 112$, to date). As reported elsewhere (Bensimon *et al.*, 2009), the overall accuracy of diagnosis was high (94%) supporting the validity of the criteria employed. Misclassification between multiple system atrophy and progressive supranuclear palsy occurred in five cases, while in 10 the final diagnosis was neither multiple system atrophy nor progressive supranuclear palsy. The most common were pathological diagnoses of Lewy body disease, amyotrophic lateral sclerosis and corticobasal degeneration. Coincident Alzheimer's pathology was observed in a number of cases with both multiple system atrophy and progressive supranuclear palsy, although not inevitably in association with cognitive impairment. Such pathology does not appear to be a major contributing feature to cognitive impairment in either the multiple system atrophy or progressive supranuclear palsy groups.

To conclude, the present study extends our understanding of the nature and natural history of cognitive impairment in patients with a clinical diagnosis of progressive supranuclear palsy or multiple system atrophy. For the first time, reliable estimates of the level of cognitive impairment are provided that support the previously described high level in progressive supranuclear palsy. Foremost, this large cohort study definitively establishes the presence of significant cognitive impairment with similar profile as in progressive supranuclear palsy in a substantial proportion of patients with multiple system atrophy at the earliest stages, with pathologically confirmed diagnosis. These findings strongly suggest that cognitive impairment should not be an exclusion criterion for the diagnosis of multiple system atrophy in research and clinical trials. Future exploration of the longitudinal data of the NNIPPS dataset should help to define and validate prospectively the rate of cognitive impairment progression in multiple system atrophy and progressive supranuclear palsy.

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Supplementary material

Supplementary material is available at *Brain* online.

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