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The prevalence of progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome) in the UK

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Summary

We performed a study to estimate the point prevalence of progressive supranuclear palsy (PSP) in the UK at national, regional and community levels. A 'Russian doll' design was used in which the population denominator for each of the three studies was successively smaller, whilst the method of case ascertainment became increasingly more rigorous. The NINDS-SPSP (National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy) diagnostic criteria for PSP were applied throughout the study for case definition. The national study identified cases using passive referral mechanisms [e.g. the British Neurological Surveillance Unit (BNSU), PSP (Europe) Association patient register]. We identified 577 cases of PSP, giving a national prevalence estimate of 1.0 per 100 000 [95% confidence interval (CI) 0.9–1.1]. The North of England regional study used active 'multiple source' case ascertainment from a collaborative network of neurologists and non-neurologists. We identified 80 cases of PSP in this study, giving a crude and age-adjusted prevalence of 3.1 (95% CI 2.4–3.8) and 2.4 (1.9–3.0) per 100 000, respectively. Of these 80 cases, 51 patients (65%) were referred initially to non-neurologists and 10 patients (13%) had not seen a neurologist at any stage of their illness. The proportion of female cases was significantly greater in the regional than in the national study (61% versus 44%; $P < 0.02$). Cases referred to non-neurologists were significantly older than those referred to neurologists in the regional study (median age 73 versus 69.5 years; $P < 0.01$). Patients in the community study were identified via diagnostic and therapeutic registers from a representative sample of general practices in Newcastle upon Tyne. We identified 17 cases of PSP, yielding crude and age-adjusted prevalences of 6.5 (95% CI 3.4–9.7) and 5.0 (95% CI 2.5–7.5) per 100 000, respectively. Seven of the 17 cases (41%) had not previously been diagnosed as PSP. This study suggests that PSP is more common than previously considered, is commonly misdiagnosed and that the majority of cases are not initially referred to neurologists. The study also confirms the importance of active and detailed case ascertainment in ensuring reliable prevalence estimates.

Keywords: progressive supranuclear palsy; Steele–Richardson–Olszewski syndrome; epidemiology; prevalence

Abbreviations: BNSU = British Neurological Surveillance Unit; NINDS-SPSP = National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy; ONS = Office of National Statistics; PACE = population-adjusted clinical epidemiology; PSP = progressive supranuclear palsy

Introduction

Progressive supranuclear palsy (PSP), also known eponymously as Steele–Richardson–Olszewski syndrome, is a progressive neurodegenerative disorder whose characteristic clinical features include a variable combination of supranuclear gaze palsy, akinetic-rigid features, early postural instability, axial dystonia and gait disturbance, and frontolimbic dementia (Steele *et al*., 1964). Retrospective clinical and clinicopathological studies have suggested a mean disease duration of between 5 and 6 years (Brusa *et al*., 1980; Maher and Lees, 1986). PSP is characterized

pathologically by abundant neurofibrillary tangles and neuropil threads in select basal ganglia and brainstem regions. These changes are associated with nerve cell loss, gliosis and occasional granulovacuolar or ballooned argyrophilic neuronal degeneration (Hauw *et al*., 1994; Jellinger *et al*., 1995).

There have been only two studies to date which have attempted specifically to determine the prevalence of PSP (Golbe *et al*., 1988; Schrag *et al*., 1999), although a number of studies, whose primary aim was to assess the prevalence of Parkinson's disease, have also reported the prevalence of PSP (de Rijk *et al*., 1995; Wermuth *et al*., 1997; Chiò *et al*., 1998). The study of Golbe and co-workers was conducted in New Jersey, USA and yielded a crude prevalence of 1.39 per 100 000 (Golbe *et al*., 1988). A passive means of case notification was used in a population of 800 000. It was assumed that all cases of PSP would have been referred to a neurologist at some time. More recently, Schrag and colleagues carried out a study based in London, UK aimed at determining the prevalence of atypical parkinsonism in a population of 121 608 (Schrag *et al*., 1999).

The authors identified six cases of PSP and reported an age-adjusted prevalence of 6.4 per 100 000 [95% confidence interval (CI) 2.3–10.6]. Such community-based studies, although extremely thorough, will, by definition, only be able to identify a small number of cases, and therefore any estimate of prevalence will be relatively imprecise. Studies of larger populations are more precise but are prone to under-ascertainment of cases. This probably explains the lower figure observed by Golbe and colleagues, although geographical variation cannot be ruled out (Golbe *et al*., 1988).

In general, all descriptive studies of PSP have to tackle a number of methodological problems including diagnostic criteria, phenotypic variability and case identification. Consensus criteria for the diagnosis of PSP were established only recently at an international workshop convened by the National Institute for Neurological Disorders and the Society for Progressive Supranuclear Palsy (NINDS-SPSP) (Litvan *et al*., 1996*a*). When the NINDS-SPSP criteria were evaluated retrospectively in a pathologically confirmed series of 83 patients, they were shown to have superior specificity, sensitivity and positive predictive value compared with existing PSP diagnostic criteria (Lees, 1987; Blin *et al*., 1990; Duvoisin, 1992; Golbe, 1993; Tolosa *et al*., 1994; Collins *et al*., 1995). Thus, the NINDS-SPSP criteria for 'probable' PSP are highly specific (100%), but lack sensitivity early in the disease course. The criteria for 'possible' PSP were felt to be suitable for descriptive epidemiological studies. Although less specific (93%), they are more sensitive, detecting 83% of patients at the first visit and within 3 years of disease onset.

Diagnostic criteria help in standardizing case definition between studies but do not reliably overcome the problem of phenotypic variability. Patients may present without, or indeed never develop, a supranuclear gaze palsy (Davis *et al*., 1985; Collins *et al*., 1995; Daniel *et al*., 1995).

False-negative clinical misdiagnosis is not uncommon, as highlighted by clinicopathological studies. For example, in one study, 6% of patients who died with a clinical diagnosis of Parkinson's disease were found to have PSP at post-mortem (Hughes *et al*., 1992). Conversely, there are pathologically confirmed cases of corticobasal degeneration, multiple system atrophy and dementia with Lewy bodies, amongst others, that were clinically misdiagnosed as PSP (false-positive clinical diagnoses) (Fearnley *et al*., 1991; Litvan *et al*., 1996*b*).

The rarity of this condition essentially eliminates door-to-door methods for case identification, although occasional cases will be identified when undertaking studies of parkinsonism. Instead, cases can be identified from multisource ascertainment methods using existing patients with a previous diagnosis of PSP or other disorders that may mimic PSP. Unfortunately, most standard hospital coding systems in the UK conventionally record diagnostic data for in-patients and not out-patient consultations. Until recently, diagnostic information was classified according to the ninth revision of the International Classification of Diseases (ICD). This version, unlike the 10th revision, classifies PSP with other disorders of the basal ganglia such as multiple system atrophy, thereby reducing the specificity of such searches. Death certification data are also an insensitive means of case identification. Maher and Lees found that PSP was only mentioned in 43% of death certificates for 30 patients with the disease. Furthermore, 27% of the patients were misclassified as Parkinson's disease (Maher and Lees, 1986).

The primary aim of the present study was to determine the point prevalence of PSP in the UK. In an effort to overcome several of the methodological difficulties described above, we used the NINDS-SPSP diagnostic criteria uniformly across three surveys undertaken at national, regional and community levels. This novel approach was used both to obtain a valid prevalence figure and to estimate the degree of, and reasons for, case under-ascertainment in larger population denominators.

Methods

Overview of study design and populations

We calculated the prevalence for PSP in three populations: the UK, a contiguous population in the North of England and in 35 general practices in Newcastle upon Tyne. We have termed this design the 'Russian doll' method as it comprises three concentric 'rings', with each inner ring having a smaller population denominator (Fig. 1). The method of case identification is more active and rigorous as the study population reduces in size. This method shares some features with the capture–recapture method (Laporte, 1994), but the latter attempts to estimate under-ascertainment within a single population rather than across different populations.

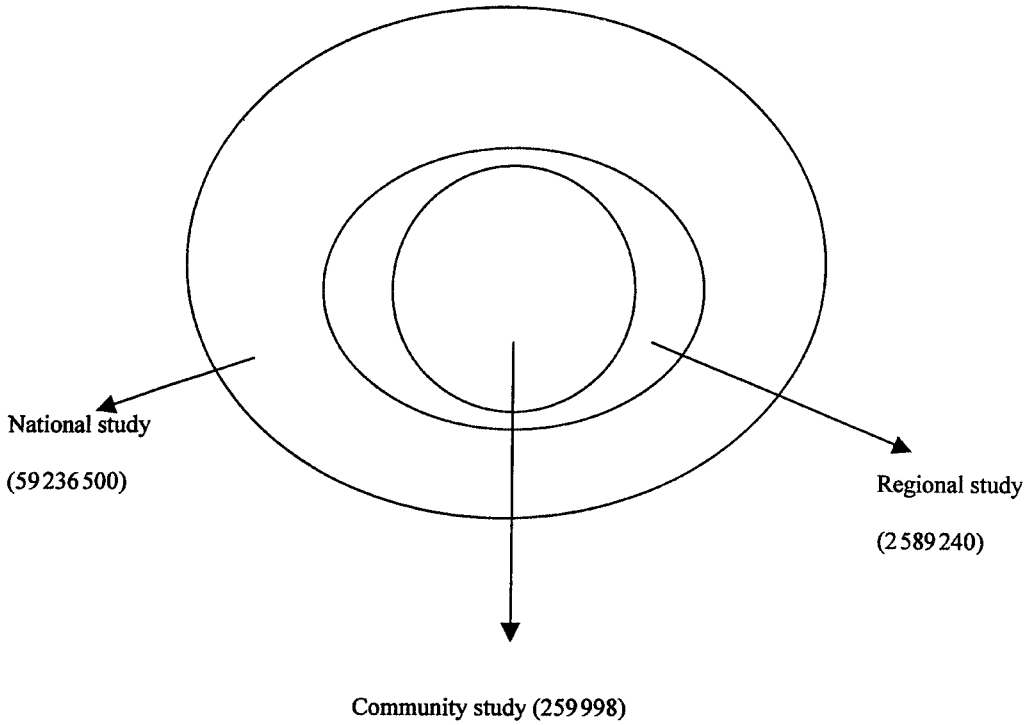

Fig. 1 The 'Russian doll model', illustrating schematically, and not to scale, the three concentric study levels and denominator populations.

Patients were diagnosed and classified as either possible or probable PSP according to the NINDS-SPSP criteria (Litvan *et al*., 1996*a*). The prevalence date for the study was 1st January 1999. Ethical approval was obtained from the Northern and Yorkshire Multi-Centre Ethics Committee and also from relevant local research ethics committees.

National study

It was not possible to use active case ascertainment methods for the national study because of the size of the population denominator. Instead, we relied upon the following sources for passive case identification.

The British Neurological Surveillance Unit (BNSU)

The BNSU is administered through the Association of British Neurologists and is intended to bring patients with rare neurological diseases to the attention of interested research groups in the UK. All consultant neurologists on the BNSU register were contacted on a monthly basis to notify the BNSU of any potential cases of PSP. Patient details were then requested from the referring neurologist in order to obtain the patient's medical records for review.

The PSP (Europe) Association

This is an active support group for patients with PSP and their carers, and maintains a register of patients. The vast majority of these cases are referred from neurologists. The medical records of all consenting patients identified from the PSP Association were requested via their consultant.

The Office of National Statistics (ONS)

This is a national body among whose functions are the collection and update of national mortality data. Mortality data were provided for all patients in the UK coded as having PSP on their death certificate.

Other sources

Consultant neurologists across the UK, particularly those with an interest in movement disorders, were invited to refer cases from their patient registers.

Cases in the national study were classified as probable or possible PSP based upon information obtained from their medical records.

Regional study

An active method of case ascertainment was used for this study, using the following sources.

Direct referral of cases

All neurologists, 'Care of the Elderly' physicians, psychogeriatricians and general physicians in the region were invited to participate and were requested to refer

any suspected case of PSP. The patient records were then reviewed.

Correspondence review

All neurologists, 'Care of the Elderly' physicians, psychogeriatricians, general physicians and their junior staff were also invited to provide *unselected* copies of *all* out-patient correspondence over a 14-month period from December 1998 to January 2000 (a total of 33 000 letters). This correspondence was reviewed by a single investigator (U.N.) to enhance complete ascertainment.

All cases from the following groups were selected: (i) cases of PSP (known or suspected); (ii) cases of parkinsonism with atypical features; (iii) unexplained falls; and (iv) unexplained eye movement disorder. All category (i) cases had their medical records reviewed. Correspondence relating to cases from categories (ii), (iii) and (iv) was requested from relevant consultants every 6 months to assess whether any further diagnostic information was available. Where insufficient information was available from the correspondence provided, the patients' medical records were reviewed. In a small proportion of cases (3%), no follow-up correspondence or medical records could be obtained.

Database screening

Regional databases were screened from the following sources: (i) gastrostomy tube register—to identify patients who were alive on the prevalence day who had undergone percutaneous endoscopic gastrostomy insertion; (ii) Parkinson's Disease Specialist Nurses; (iii) Physician case registers; (iv) Movement Disorder clinic register; (v) Department of cardiovascular medicine in the elderly out-patient register—to identify patients undergoing autonomic function studies in the context of unexplained falls (this is routine practice in Newcastle where there is a strong research interest in falls in the elderly); and (vi) Regional cognitive clinic register (held by the Department of Psychogeriatric Medicine). In each case, screening took place according to a standardized format designed to identify potential cases of PSP.

In-patient hospital sources

Each neurology department in the region allowed one investigator (U.N.) access to the records of academic neurology meetings held during the preceding 5 years. The Regional Health Authority provided records of all patients admitted to hospital with a diagnosis of PSP according to the ICD 10 coding system (G23.1).

Cases in the regional study were diagnosed as probable or possible PSP according to a review of their medical records. In addition, however, cases were also personally examined whenever possible.

Community study

An intensive two-part active case ascertainment process was used in this study. Initially, the computerized records of participating general practices were screened for patients over 40 years of age with the following entries: 'Parkinson's disease'; 'parkinsonism'; 'progressive supranuclear palsy'; 'Steele–Richardson–Olszewski syndrome', as well as for those patients who had ever been prescribed either a levodopa-containing drug or amantadine. The practice records of all patients thus identified were reviewed. Missing records were reviewed at a second visit. Hospital records were used where insufficient information was available from the general practice source. If patients were deceased or had registered with a different general practitioner, their records were requested from the Tyne and Wear Contractor Services Agency.

Patients were excluded from further study if they had used the listed medications for other indications, their records had been miscoded or the onset of their parkinsonian symptoms was within 6 months of treatment with a dopamine receptor blocking agent. Patients were also excluded if features were recorded which would exclude PSP according to the NINDS-SPSP criteria.

Patients were included in the next phase of the study if the following criteria were met: the presence of parkinsonism and *either* an absent or unsustained response to levodopa *or* any additional atypical features such as early falls, eye movement disorder or early bulbar problems. Those patients who fulfilled these criteria were invited by letter via their general practitioners to attend the Royal Victoria Infirmary for further assessment, or to be seen at home. Reminder letters were sent to patients who did not reply after a month, and patients who still failed to respond were telephoned at home.

All patients who agreed to be seen underwent a structured interview, clinical examination and were also videotaped for later review and diagnostic identification. All gave informed consent to participate in the survey.

Statistical methods and data analysis

A specially designed database (Creative Computer Consultants Ltd) was used for data entry. This database included an algorithm for assessment of whether each case conformed to the NINDS-SPSP criteria for PSP. It also had an 'audit trail' function, which allowed recording of the same item of data from a variety of sources (e.g. medical records and clinical assessment), thus permitting data quality to be monitored. Furthermore, cases identified from more than one source were highlighted within the database, thereby avoiding duplication of data. The results of the database were checked regularly for internal inconsistencies by comparing the diagnoses assigned by the algorithmic database in a random sample of cases with those of the investigators.

Cases were included in the prevalence analysis if they

Table 1 *Ascertainment data for national, regional and community studies*

Study	Source	No. of cases	Population denominator
National	BNSU	71	
	PSP Association	431	
	Regional study	88	
	Neurologist registers	16	
	Duplicates	29	
	Total PSP cases	577	59 236 500
	Records reviewed	198	
	Classified PSP cases	187	
Regional	Direct referral	35	
	Correspondence review	41	
	Databases	17	
	Community study	17	
	Duplicates	30	
	Total PSP cases	80	2 589 240
Community	Total PSP cases	17	259 998

conformed to the NINDS-SPSP diagnostic categories for possible or probable PSP, were alive and suffering from PSP on 1st January 1999, and were permanently resident within the predetermined study populations (the UK, North of England population and participating practices in Newcastle upon Tyne). Denominator data for the population at risk were derived from the mid-1998 census figures for the UK population and that of the Northern population, and from the Newcastle and North Tyneside Health Authority for participating general practices.

To examine the relative efficiency of using different methods of case identification, we recorded the number of records that were either screened or were reviewed in detail. We have assumed that, on average, a screened record took 1 min, whilst a record review took 15 min. Using these figures, we therefore calculated the number of hours needed to find a single case ('NNF') using different modes of case identification.

Statistical comparisons were made using either the chi-squared test or 95% CIs to detect differences in proportions for categorical variables. The Mann–Whitney *U* test was used to compare continuous variables. The calculation of 95% CIs using crude rates was based on the Poisson distribution. Age-adjusted rates were calculated by direct standardization to the hypothetical European population (Esteve *et al*., 1994). To compare our community prevalence rate with a previous community study (Schrag *et al*., 1999), direct age-standardized rates were calculated using the same European population, and Poisson regression was used to calculate the age-adjusted prevalence ratio and 95% CI.

Results

National study

We identified 577 cases of PSP on the prevalence day (Table 1). The PSP Association register identified 431 cases,

Table 2 *Demographic data for confirmed PSP cases across national, regional and community studies*

Study	No. of cases	Sex ratio (M : F) (% female)	Probable : possible PSP	Median age (range)	Median age at onset (range)	Median years of disease duration (range)	Median years of duration onset to death (range)
National (records reviewed)	187	91 : 96 (51)	1.4 : 1	72 (46–88)	66 (41–83)	4 (0–20)	5 (1–17)
Cases identified solely from national study	107	60 : 47 (44)	1.3 : 1	72 (46–84)	65 (41–80)	4 (0–20)	5.5 (4–15)
Regional	80	31 : 49 (61)	1.7 : 1	72 (52–88)	69 (48–83)	3 (0–14)	4.5 (1–17)
Cases identified solely from regional study	72	28 : 44 (61)	1.6 : 1	71 (54–88)	69 (49–81)	3 (0–13)	4 (1–17)
Community study	17	8 : 9 (53)	1.8 : 1	72 (52–88)	67 (48–83)	4 (2–15)	5 (5–6)

Table 3 *Crude, sex-specific and age-adjusted prevalence for national, regional and community studies*

Study	No. of cases/ (population)	No. of male cases/ (population)	No. of female cases/(population)	Crude prevalence (95% CI)	Sex-specific prevalence (95% CI)	Age-adjusted prevalence (95% CI)
National (all cases)	577/59 236 500	296/29 128 391	285/30 108 109	1.0 (0.9–1.1)	1.0 (0.9–1.1) (M) 1.0 (0.8–1.1) (F)	*
National (clinically confirmed cases)	187/59 236 500	91/29 128 391	96/30 108 109	0.3 (0.3–0.4)	(2.5–3.8) (M) (2.6–3.8) (F)	0.3 (0.2–0.3)
Regional	80/2 589 240	31/1 268 187	49/1 321 053	3.1 (2.4–3.8)	2.4 (1.6–3.3) (M) 3.7 (2.7–4.8) (F)	2.4 (1.9–3.0)
Community	17/259 998	8/129 383	9/130 615	6.5 (3.4–9.7)	6.2 (1.9–10.5) (M) 6.9 (2.4–11.4) (F)	5.0 (2.5–7.5)

*Unable to calculate due to missing data on age.

while the BNSU identified 71 cases, 88 were identified from the regional study and a further 16 were found from neurologists' patient registers. Twenty-nine cases were identified from more than one source. We were able to obtain only 198 of the 577 (34%) medical records for review. Of these 198 cases, 187 (94%) were classified as having PSP. A total of 108 of the 198 patients (54%) whose notes were reviewed fulfilled NINDS-SPSP criteria for probable PSP, while 79 (40%) were categorized as possible PSP. In the remaining 11 cases (6%), the diagnosis of PSP was excluded. The median age of the 187 patients classified as either probable or possible PSP was 72 (range 46–88) years (Table 2). Ninety-six of the 187 patients (51%) were female. Of the 187 cases, 20 had died subsequent to the prevalence day. The median disease duration from onset to death in these patients was 5 (1–17) years. Median disease duration in the living patients was 4.0 (0–20) years.

The national prevalence figure for all 577 identified cases in a population of 59 236 500 was 1.0 per 100 000 (95% CI, 0.9–1.1). Restricting the analysis to PSP cases confirmed by record review reduced the crude prevalence to 0.32 (95% CI 0.27–0.36) per 100 000 and the age-adjusted prevalence to 0.25 (95% CI 0.21–0.29) per 100 000 (Table 3). It was not possible to calculate the age-adjusted rate for the complete national sample as the age of cases was not always available.

Regional study

We identified 80 cases of PSP in the regional study, resulting in a crude and age-standardized prevalence rate of 3.1 (95% CI 2.4–3.8) and 2.4 (95% CI 1.9–3.0) per 100 000, respectively (Table 3). Sixty of the 80 patients (75%) were examined by one of the investigators during the study. Fifty cases were classified as probable PSP and 30 were classified as possible PSP. The median age of the 80 patients classified as either probable or possible PSP was 72 (52–88) years (Table 2). Forty-nine of the 80 patients (61%) were female. Of the 80 cases, 12 had died after the prevalence day. The median disease duration from onset to death in these patients was 4.5 (1–17) years. Median disease duration in the living patients was 3.0 (0–14) years.

Table 4 *Referral patterns for PSP cases identified in the regional study*

Specialist to whom case was referred by GP	No. of cases (%)	No. of cases later seeing a neurologist
Neurologist	28 (35)	N/A
Non-neurologist	51 (64)	41
Data unavailable	1 (1)	N/A
Total	80	N/A

N/A = not applicable.

Details of the hospital specialist to whom the patient was first referred are shown in Table 4. Of the 51 non-neurological specialists who were first referred PSP patients, 32 (63%) were 'Care of the Elderly' physicians. The 28 patients who were first referred by their GP to a neurologist were significantly younger than the 32 first referred to a 'Care of the Elderly' physician (median age 69.5 versus 77.5 years; Mann–Whitney test, $P < 0.001$). The median age at onset in the cases first referred to a neurologist was also significantly earlier (63.0 versus 71.0 years; Mann–Whitney test, $P < 0.001$). Ten of the 80 PSP cases (13%) had not seen a neurologist at any stage of their illness.

Of these 80 patients, 35 were identified by direct referral, 41 were detected from review of out-patient correspondence, 17 were identified from regional databases and a further 17 cases were identified from the community study (Table 1). Thirty cases were therefore identified from more than one source. The efficiency of detecting cases according to data source is also shown in Table 5. Although in most cases PSP could be excluded using the clinical details provided by each source, a proportion of cases required record review. Direct referral gave the highest yield of identified cases, but reliance on this source alone would have detected only 35 (43%) of all cases. A total of 27 of the 38 cases directly referred to the study from neurologists, and eight of the 28 cases referred from 'Care of the Elderly' physicians were found subsequently to have PSP.

Table 5 *Yield of PSP cases identified from each source in the regional and community studies*

Primary source needed	No. of records screened*	No. of records reviewed†	No. of PSP cases	No. of hours to find a case
Direct referral				
Neurologist		38	27	0.4
Geriatrician		28	8	0.9
Correspondence review	33 000	100	41	14.0
Databases	1868	60	17	2.7
Community study	259 998‡	397	17	5.8

*1 min per record; †15 min per record; ‡screened by computer, and so not included in calculation.

Table 6 *Cases identified in the community study and reasons for exclusion from further assessment*

Exclusion criterion	No. of records
Idiopathic Parkinson's disease with sustained levodopa response	96
Drug-induced parkinsonism	54
Miscoded	6
Alzheimer's disease	4
Cerebrovascular parkinsonism	3
Dementia with Lewy bodies	4
Essential tremor	4
Drug used for other indications, e.g. multiple sclerosis, influenza	17
Total	188

Community study

We approached 42 general practices, and 35 (83%) agreed to participate in the study. The consenting and non-consenting practices had populations with similar age and sex distributions (data not shown). The screening of all patient registers identified 490 potential patients. Practice records were available for review in 397 (81%) of these cases. Included in the 93 unavailable practice records were three patients who did not wish to participate, 13 cases who had died and a further four cases who had changed practice to one outside Newcastle. Of the 397 cases whose records were reviewed, 188 (47%) were found to be ineligible for further study. Reasons for ineligibility are listed in Table 6. The remaining 209 patients were invited for further assessment. Of these patients, 193 (89%) agreed to take part in the study, while 12 subjects declined to participate and a further four subjects were untraceable. A further 22 of the 193 consenting cases died before they could be seen, leaving a total of 171 potential cases to be examined clinically. The patients who could not be assessed were significantly older ($P < 0.005$) than those who were seen, although the sex distribution was not significantly different ($P = 0.91$).

Seventeen of the 171 cases (10%) fulfilled NINDS-SPSP criteria for PSP. Eleven cases were classified as probable PSP and six as possible PSP. The median age of the 17 patients was 73 (52–88) years (Table 2). Nine of the 17 patients (53%) were female. Of the 17 cases, two had died after the prevalence day. The median disease duration in the 15 living patients was 4.0 (2–15) years. Fifteen of the PSP cases were identified using therapeutic registers, with two additional cases identified by diagnostic registers.

The crude and standardized age-adjusted prevalences for PSP were 6.5 (95% CI 3.4–10.0) and 5.0 (95% CI 2.5–7.5) per 100 000, respectively (Table 3). The latter figure is identical, after rounding, to the prevalence rate of 5.0 (95% CI 0.9–9.2) per 100 000 of Schrag and colleagues (Schrag *et al*., 1999), after standardizing to the same population. The wider confidence interval for the latter study reflects the smaller number of identified cases. The prevalence ratio comparing both studies was 1.0 (95% CI 0.4–2.4).

The crude PSP prevalence figures for men and women were 6.2 (95% CI 1.9–10.5) and 6.9 (95% CI 2.4–11.4) per 100 000, respectively. If median survival for PSP is taken to be 5.6 years (Litvan *et al*., 1996*c*), an indirect age-adjusted incidence of PSP may be calculated as 0.9 cases per 100 000 per year from our standardized prevalence data.

Seven of the 17 PSP cases had been misdiagnosed prior to the study as idiopathic Parkinson's disease (three cases), cerebrovascular pseudoparkinsonism (three cases) and normal pressure hydrocephalus (one case) (Table 7). In addition to these 17 cases with PSP, a further 10 cases were seen with parkinsonism and atypical features who did not fulfil criteria for another specific parkinsonian disorder. Of the 171 patients (88%) who were clinically assessed, 152 had parkinsonism. All patients with PSP in the community study had akinetic rigid features and, amongst the total of 152 patients with parkinsonism, patients with PSP and those with unclassified atypical parkinsonism therefore contributed 11% (17/152) and 7% (10/152) of cases, respectively.

To examine the representativeness of cases identified across the various studies, we examined whether certain demographic features differed as an indication of biased ascertainment as compared with underascertainment (Table 2).

The age at onset, disease duration and current age of cases were similar for the national, regional and community studies. There was a greater number of male cases in the national study compared with the regional study (60 out of 107; 56% versus 31 out of 80; 39%, $P < 0.02$). The ratio of probable

Table 7 *Demographic and clinical characteristics of community PSP cases*

Patient	Age (years)	Sex	Age at onset (years)	Disease duration (years)	Symptoms at onset	Pre-study diagnosis	Response to levodopa	NINDS-SPSP category
1	88	M	73	15	Slow unsteady	CVD	Nil	Possible
2	83	F	74	9	Unsteady	IPD and dementia	Poor	Probable
3	76	F	69	7	Tremor left arm	IPD	Nil	Probable
4	72	F	67	5	Falls	CVD	Poor	Probable
5	56	M	48	8	Falls and slowness	PSP	Moderate	Possible
6	70	F	67	3	Falls and behaviour change	PSP (?)	Minimal	Probable
7	73	M	71	2	Falls	NPH	Minimal	Probable
8	66	M	58	8	Falls, blurred vision, bulbar Sx	PSP	Nil	Probable
9	62	F	54	6	Postural instability, diplopia	PSP	Minimal	Possible
10*†	76	F	71	5	Falls	PSP	NT	Probable
11	70	F	65	5	Resting tremor	PSP	Minimal	Possible
12†	76	M	71	5	Falls, reduced speech output	PSP	Nil	Probable
13	87	F	83	4	Mild left action tremor	CVD	Minimal	Probable
14	52	M	50	2	Falls	PSP	Never tried	Probable
15	72	M	69	3	Falls	PSP	Declining	Probable
16+	73	M	67	6	Left sided tremor	PSP	Nil	Possible
17	83	F	80	3	Falls	IPD	Nil	Possible

CVD = cerebrovascular disease; IPD = idiopathic Parkinson's disease; NPH = normal pressure hydrocephalus; NT = not tolerated; Sx = symptoms. *Patient not examined by study investigators; †patient deceased after prevalence day.

to possible PSP cases was higher for cases identified by the regional study than from the national study (1.7 : 1 versus 1.3 : 1).

Discussion

National study

We estimated a crude prevalence for PSP of 1.0 (95% CI 0.9–1.1) per 100 000 from the 577 cases identified in the national study. By virtue of the large population covered (59 236 500) and the passive means of case ascertainment, our *a priori* hypothesis was that this study component would significantly underestimate the prevalence of PSP.

The study of Golbe and colleagues in 1988 was the first to assess PSP prevalence specifically (Golbe *et al*., 1988). They reported this to be 1.4 (95% CI 0.7–2.5) per 100 000. The authors used a system of passive case surveillance, and no physicians other than neurologists were involved in the study. The NINDS-SPSP international criteria for PSP definition were not available at the time of the study and the authors used their own diagnostic criteria for PSP, formulated for maximum specificity, rather than sensitivity. Due perhaps to the mobile nature of the population, only 27% of identified cases were in the study area on the prevalence day. The authors recognized their own estimate as a minimum prevalence figure.

Our national study has a number of similarities to the work of Golbe and colleagues. In particular, it is limited by the failure to involve non-neurologists fully and by its passive surveillance design. Interestingly, the prevalence in our national study of 1.0 per 100 000 is of the same order as that reported by Golbe (1.4 per 100 000). Our national study was also limited by the fact that in two-thirds of the cases identified, the medical records were not available to confirm the diagnosis.

Extrapolation of community study prevalence data to the national study would suggest that the latter should have identified ~3000 cases and may therefore have failed to identify the majority (81%) of PSP cases in the UK. Nevertheless, we believe that the 577 cases actually ascertained in the national study represent the largest cohort of PSP cases identified to date. The validity of this figure is limited, because most of the case records were not available for review. The majority of cases (75%) were identified from the PSP Association compared with 12% from the BNSU. Only 19 cases (3%) were identified from both sources. One explanation for this finding could be that patients who are diagnosed by neurologists are not then routinely reviewed by them.

One of the difficulties encountered in the use of the NINDS-SPSP criteria during our record-based analysis was the lack of information pertaining to the date of onset of falls. For a patient to be classified as probable PSP according to these criteria, they must have prominent postural instability, with falls in the first year of disease onset (Litvan *et al*., 1996*a*) (see Appendix I). This resulted in many cases, clinically very characteristic of PSP, being classified as possible cases.

We were able to confirm the diagnosis of PSP according to the NINDS-SPSP criteria in the vast majority of cases

Table 8 *A summary of prevalence data for progressive supranuclear palsy*

Author	Year of report	Geographical area studied	Population denominator	Crude prevalence (per 100 000)
Golbe	1988	New Jersey, USA	799 022	1.39
De Rijk	1995	Rotterdam, The Netherlands	6969	14.3*†
Wermuth	1997	Faroe Islands	43 709	4.6*
Chio	1998	Northwest Italy	61 830	3.2*
Schrag	1999	London and Kent, UK	121 608	4.9

*These studies were designed primarily to ascertain the prevalence of idiopathic Parkinson's disease. Diagnostic criteria for PSP were not stated. †Only persons aged 55 years or older were included.

referred by neurologists, suggesting that PSP is diagnosed accurately by neurologists. An alternative explanation, however, may be that early (and not clinically 'full blown') cases, or phenotypic variants, were less likely to be referred. It is notable that Litvan found that the first visit to a tertiary centre was 1.5–3.7 years after the onset of PSP symptoms (Litvan *et al*., 1996*c*), a range in close agreement with the median interval reported by Maher and Lees of 3 years (Maher and Lees, 1986). Thus, the average patient with PSP may remain undiagnosed for approximately half of the natural history of their disease.

Regional study

According to the prevalence estimate provided by our national study, we would have predicted 25 cases of PSP within the regional study population. The 80 cases actually identified confirm the increased sensitivity of the regional study and give an age-adjusted standardized prevalence of 2.4 (95% CI 1.9–3.0) per 100 000. Extrapolating prevalence data from the community study, however, predicts that we should have detected 130 cases, suggesting that only two-thirds of the regional PSP cases were identified. Table 5 indicates the large number of potential cases screened and found not to have PSP, confirming a low specificity for the multiple source, active case ascertainment technique. Nevertheless, each potential source of cases was fruitful, with a review of unselected out-patient correspondence yielding the highest number of cases although at the greatest cost in terms of hours needed per case. It also identified cases earlier in the patient's disease course (3 versus 4 years, $P < 0.002$). Sixty-five per cent of regional PSP cases were first referred to non-neurologists and 13% of cases had not seen a neurologist at all.

Not surprisingly, patients referred to neurologists were younger than those referred to 'Care of the Elderly' physicians (median age 69.5 versus 77.5 years) with an earlier median age at onset (median age at onset 63.0 versus 71.0 years). This highlights the potential bias of studies recruiting cases only from neurologists. Similarly, significantly more female cases were identified from the regional study compared with the national study (61% versus 44%), highlighting potential gender bias when ascertaining cases solely from neurological specialist centres.

A potential criticism of the regional study was our failure to examine 25% of the identified cases personally. We therefore relied upon the application of the NINDS-SPSP diagnostic criteria to the medical records alone in these cases. We do not believe, however, that this will have had a significant effect upon diagnostic specificity, as the remaining 60 cases diagnosed as PSP based upon record review were all confirmed to have PSP on subsequent examination.

The methodology used in our regional study shares similarities with the PACE (population-adjusted clinical epidemiology) technique. The latter method extends a regional collaborative network beyond specialist centres, thereby increasing cohort size and reducing bias (Proctor and Taylor, 2000). Both the method employed in the current study and the PACE technique, however, would fail to identify undiagnosed or misdiagnosed cases and those patients who are managed solely in a primary care setting. Furthermore, patients discharged from routine follow-up and cases first referred to other specialists not involved in the study would have been overlooked. It is of interest that the regional study methodology alone would have failed to identify eight of the 17 community study cases.

Community study

Our age-adjusted standardized prevalence figure for PSP from this study was 5.0 (95% CI 2.5–7.5). Newcastle upon Tyne has both a large and a stable population. Both factors will have contributed to the accuracy of our prevalence estimate. Nevertheless, the relatively wide confidence intervals reflect the small number of cases that were identified ($n = 17$).

There are a few other studies with which one can compare these results (Table 8). A door-to-door study of parkinsonism in the elderly from Rotterdam found a single case of PSP in a population of 6969 over 55 years of age, giving a prevalence of 14.3 per 100 000 over 55 years (95% CI 0.4–80.4) (de Rijk *et al*., 1995). This is less than our prevalence rate of 25.6 (95% CI 14.6–41.6) per 100 000 over 55 years, but these differences may simply reflect chance, as indicated by the marked overlap for the respective confidence intervals. Two further studies of Parkinson's disease, using multiple sources of case ascertainment including medication use, have also incidentally reported prevalence data for PSP (Wermuth *et al*., 1997; Chiò *et al*., 1998). In neither report did the

authors state the diagnostic criteria used for PSP. Wermuth and co-workers identified two cases of PSP in the Faroe Islands, with a population denominator of 43 709, giving a prevalence of 4.6 (95% CI 0.5–16.5) per 100 000 (Wermuth *et al*., 1997). A later Italian study reported a prevalence for PSP of 3.2 (95% CI 0.4–11.7) per 100 000 (Chiò *et al*., 1998).

Our study is most similar, methodologically, to that by Schrag and colleagues. This was also a community-based study (population 121 608) derived from primary care and utilizing sensitive inclusion criteria (Schrag *et al*., 1999). This study also used the NINDS-SPSP criteria with personal examination in almost all suspected patients. Patients developing dementia prior to onset of parkinsonism were excluded.

This may have led to under-ascertainment of cases of PSP, a fact recognized by the authors. Since we did not screen for all antiparkinsonian drugs, or for isolated tremor, the proportion of cases reviewed to those screened is lower than in the study of Schrag and co-workers. We did not exclude specifically cases in whom dementia appeared to present before parkinsonism. Significant cognitive impairment may be an early feature of PSP (Pillon and Dubois, 1992). Neither study would have identified cases of PSP presenting with falls but without parkinsonism, or cases not yet seen by their general practitioner. Our age-adjusted prevalence rate for PSP is identical to that reported recently by Schrag and co-workers (Schrag *et al*., 1999). However, both rates are again based on relatively small numbers of cases. Although these data support the notion that there is no marked geographic variation between the North and South of England, one must be cautious with this interpretation as the confidence interval around the prevalence ratio is wide.

Our community study indicates that PSP is often misdiagnosed. Forty-one per cent of the 17 cases we identified had alternative diagnoses prior to the study. The most common misdiagnoses were Parkinson's disease (three cases) and cerebrovascular disease (three cases). A further case was diagnosed initially as having normal pressure hydrocephalus, but had failed to respond to lumbar puncture. Many of the features of PSP, including falls, bulbar dysfunction and hyperreflexia, may be present in cerebrovascular disease, while normal pressure hydrocephalus can present with gait disturbance, subcortical dementia and so-called 'lower body parkinsonism'. In 16 of the 17 cases, levodopa medication had been prescribed at some stage of the illness. Only one patient was described as having had a 'moderate' response, while the others had shown no or 'minimal' improvement with this therapy.

In conclusion, we have demonstrated that there are potentially 20-fold variations in crude prevalence rates of PSP depending on the methods of case finding and size of the surveyed population. Studies identifying cases diagnosed solely by neurologists will not only underestimate the prevalence but will also bias cases towards being male with a younger age at onset. This may also influence conclusions about the natural history of disease, but as yet our data cannot answer this. Since the disease exhibits broad phenotypic variability, clinicopathological correlation, particularly for possible cases of PSP, is of paramount importance. Our best estimate of the true prevalence, from the community study, is almost identical to that from Schrag and colleagues (Schrag *et al*., 1999), supporting their conclusion that the prevalence of PSP has been underestimated in the past and has similar rates for both the North and South of England. Further follow-up of our clinical cohort of cases will enable us to examine the natural history of this disease in greater detail and its impact on quality of life.

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Appendix I *NINDS-SPSP clinical criteria for the diagnosis of PSP**

PSP	Mandatory inclusion criteria	Mandatory exclusion criteria	Supportive criteria
Possible	Gradually progressive disorder. Onset at age 40 or later with either vertical (upward or downward gaze) supranuclear palsy or both slowing of vertical saccades and prominent postural instability with falls in the first year of disease onset. No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria	Recent history of encephalitis. Alien limb syndrome, cortical sensory deficits, focal frontal or temporo-parietal atrophy. Hallucinations or delusions unrelated to dopaminergic therapy. Cortical dementia of Alzheimer's type (severe amnesia and aphasia or agnosia, according to NINCDS-ADRA criteria). Prominent early cerebellar symptoms or prominent early unexplained dysautonomia (marked hypotension and urinary disturbances). Severe asymmetric parkinsonian signs, i.e. bradykinesia. Neuroradiological evidence of relevant structural abnormality, i.e. basal ganglia or brainstem infarcts, lobar atrophy. Whipple's disease, confirmed by polymerase chain reaction, if indicated	Symmetric akinesia or rigidity, proximal more than distal. Abnormal neck posture, especially retrocollis. Poor or even absent response of parkinsonism to levodopa therapy. Early dysphagia and dysarthria. Early onset of cognitive impairment including at least two of the following: apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitation behaviour, or frontal release signs
Probable	Gradually progressive disorder. Onset age 40 or later. Vertical (upward or downward gaze) supranuclear gaze palsy and prominent postural instability with falls in the first year of disease onset. No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria	As above	As above
Definite	Clinically probable or possible PSP *and* histopathological evidence of typical PSP	As above	As above

*Adapted from Litvan *et al*. (Litvan *et al.*, 1996*a*).