

Prevalence of Progressive Supranuclear Palsy and Corticobasal Syndrome in Scotland

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Keywords

Progressive supranuclear palsy · Corticobasal degeneration · Corticobasal syndrome · Prevalence · Epidemiology

Abstract

Introduction: We estimated the point prevalence of progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) at regional and national levels in Scotland, UK, as there are few high-quality prevalence studies of these conditions. **Methods:** Nationally, multiple methods of case ascertainment were used including clinician and nurse specialist referral, searches of ICD-10 diagnostic coding in routinely collected electronic health data (Scottish Morbidity Record), and patient self-referral. In one region, we also searched GP databases and unselected hospital correspondence. Cases were verified by clinical examination or medical record review. National and regional total and age-sex-stratified crude prevalence rates on December 31, 2018, were calculated. **Results:** The regional crude point prevalence was 4.28 per 100,000 (95% CI 2.90, 6.31) for PSP and 2.05 per 100,000 (95% CI 1.17, 3.59) for CBS. The national crude prevalence rates were lower due to the greater reliance on passive case ascertainment. There were no clear sex differences. At a national level, the peak crude prevalence rate for both PSP and

CBS was in the 70–79 age group. **Discussion:** The prevalence rates of PSP and CBS were similar to previous estimates with little change over the past 20 years.

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Published by S. Karger AG, Basel

Introduction

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are neurodegenerative diseases that share pathological and clinical features [1]. Diagnosing pathologically proven CBD is difficult because various pathologies cause similar clinical findings, so it is now best viewed as corticobasal syndrome (CBS). Prevalence studies are important for estimating the burden of disease in a population. There are however few good prevalence studies of PSP and CBS and none conducted in Scotland, UK [2].

Methods

Case Ascertainment

Multiple, overlapping methods of case ascertainment were used. A “Russian doll” design was employed, whereby methods of ascertainment were more rigorous as the population denominator reduced from national to regional levels [3].

After promoting the study at departmental, regional, and national meetings, all relevant clinicians (neurology, old-age psychiatry, geriatrics, Parkinson's nurse specialists) in Scotland were emailed monthly (January 2018 to February 2019) to request notification of prevalent cases. Scottish inpatient healthcare data for general (SMR01) and psychiatric admissions (SMR04) were searched to identify individuals with potentially relevant ICD-10 codes (see Appendix) from February 2011 to July 2019 (capturing delayed coding). The Association of British Neurologists Rare Diseases Ascertainment and Recruitment scheme, which was simultaneously recruiting people with CBS in the UK, was asked to share Scottish cases. People with PSP/CBS were identified from the PSP Association charity database of individuals who had consented to contact about research. Patients could also self-refer until February 2019 via study information presented on the PSP Association, Scottish Dementia and Neurodegenerative Disease network, and the Join Dementia Research network websites and through public engagement events.

Two additional methods were restricted to NHS Grampian due to resource and time constraints. All people in the UK are provided with free primary care services by being registered with a local General Practice (GP) service. In the UK, most patients' first healthcare professional contact is therefore with their primary care provider. GPs also receive all secondary (hospital) care outpatient clinic letters and inpatient discharge summaries. All GP services in NHS Grampian were therefore contacted in 2018 to request notification of relevant people and searches of their practice databases for those assigned relevant READ codes (see Appendix). Neurology, geriatrics, and old-age psychiatry outpatient and inpatient hospital letters stored on the Electronic Clinical Communications Implementation (ECCI) Programme system were searched (January 2015 to December 2018) using Structured Query Language for the phrases "progressive supranuclear palsy," "corticobasal degeneration," "corticobasal," "supranuclear," "PSP," and "CBD."

Definition of Cases and Prevalence

Due to privacy concerns, the Public Benefit and Privacy Panel (PBPP) prohibited us from contacting identified cases to verify diagnoses. However, due to a concurrent prospective national cohort study, in which individuals with PSP/CBD consented to clinical examination and/or medical record review, we verified a proportion of identified prevalent cases nationally. The 1996 NINDS-SP-SP diagnostic criteria [4] for PSP and Armstrong's criteria [5] for CBD were used. For those not seen in the cohort study and where their medical record was unavailable, the named consultant was contacted to clarify diagnoses.

People were deemed prevalent if they had a diagnosis of PSP or CBS and were alive and resident within the study population on the prevalence day, December 31, 2018. Clinicians were contacted 12 months after the prevalence date to confirm that previously notified cases had not undergone diagnostic revisions and that they were alive and resident in the same region on the prevalence day.

Data Analysis

Details of each identified person were entered into a single database, and duplicates removed. The population denominator data were derived from the most recent national and regional population estimates from the National Records of Scotland [6]. National and regional overall and age-sex-specific prevalence rates were calculated, with 95% confidence intervals for point prevalence rates calculated based on the Poisson distribution.

The study was approved by the national Caldicott guardian and PBPP and did not require patient consent. It is reported in line with the Standards of Reporting of Neurological Disorders guideline [7].

Results

Case Ascertainment

From 220 clinician (predominantly neurologists and geriatricians) or nurse specialist referrals received nationally, 200 unique people were identified over the prevalent period (Fig. 1). Nationally, 14,718 healthcare episodes in SMR01 and 1,165 healthcare episodes in SMR04 with the candidate ICD-10 diagnostic codes were identified, resulting in 1840 and 514 individuals who were alive on the prevalence day. Due to the high specificity of the G23.1 ICD-10 code for PSP, attempts were made to contact the clinical team of all 105 identified individuals (SMR01 $n = 102$, SMR04 $n = 3$) assigned this code, and a clinical diagnosis of PSP was confirmed in 84. In the remainder, we were unable to verify the diagnosis due to non-response from the responsible clinician or a revised clinical diagnosis. Due to non-specificity and the large numbers of individuals assigned each of remaining ICD-10 diagnostic codes across Scotland, we restricted clinical verification to NHS Grampian, Highland, Orkney, and Shetland, where we had access to clinical records. Of the 331 individuals assigned the remaining ICD-10 diagnostic codes in those health boards, who were alive on the prevalence day, seven prevalent PSP/CBS cases were identified (all from SMR01). Fifteen individuals registered their interest in being contacted about research opportunities with the PSP Association or self-referred.

Regionally, 44 of 75 general practices in NHS Grampian supplied data (24 individuals), of whom 14 had PSP/CBS ($n = 15$ in Fig. 1 as one GP referral was received from outside NHS Grampian). The ECCI database generated 1,210 records for review, from which 179 potentially relevant records were identified, leading to identification of 34 people with PSP/CBS.

Of 413 identified people, 127 were identified by more than one method of case ascertainment (two methods $n = 108$, three $n = 13$, four $n = 6$). Clinician/nurse specialist referral gave the highest yield of identified cases, followed by the SMR01 (predominantly the G23.1 code) (Fig. 1).

Prevalence Rates

Across Scotland, 134 people with PSP (52.2% men) and 47 with CBS (48.9% men) were alive on the preva-

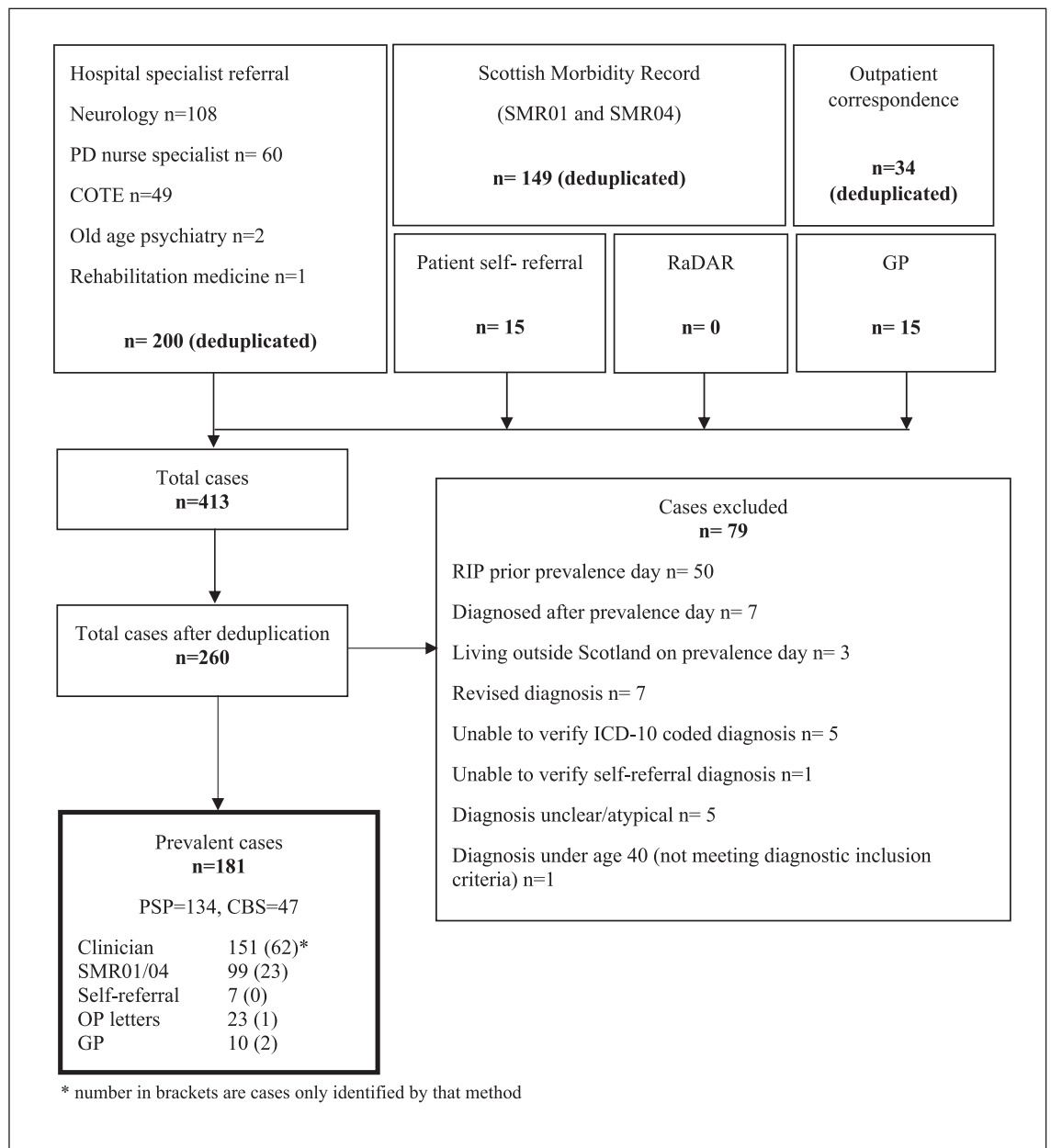


Fig. 1. Flow diagram showing source of prevalent cases.

lence day, giving national crude prevalence rates of 2.46 (95% CI 2.08, 2.92) per 100,000 and 0.86 (95% CI 0.65, 1.15) per 100,000, respectively. In Grampian, where there was additional case ascertainment, the crude rates were higher: PSP 4.28 (95% CI 2.90, 6.31) per 100,000 and CBS 2.05 (95% CI 1.17, 3.59) per 100,000 (Table 1).

Nationally, 32.8% of people with PSP and 51.1% with CBS were examined, whilst in Grampian, it was 48.0% and 58.3%, respectively, though all Grampian cases were

verified by case note review. Of the 12 persons with CBS in Grampian, 1 person was assigned a definite diagnosis (post-mortem); 3, probable; and 8, possible. Of 25 persons with PSP, 1 received a definite (post-mortem) diagnosis; 15, probable; and nine, possible.

There were no clear trends to suggest sex differences in the prevalence of PSP or CBS. The prevalence rate for both PSP and CBS increased with age, peaking in the 70–79 age group nationally.

Table 1. Age- and sex-stratified crude prevalence rates per 100,000 across Scotland and in Grampian

		Case frequency						Age-stratified crude prevalence (95% CI) per 100,000						
		40–49 years	50–59 years	60–69 years	70–79 years	80–89 years	≥90 years	40–49 years	50–59 years	60–69 years	70–79 years	80–89 years	≥90 years	total
Scotland (5,438,100)														
Total	PSP	0	4	34	75	20	1	0.00	0.51 (0.20, 1.30)	5.34 (3.82, 7.46)	16.2 (13.0, 20.3)	9.02 (5.84, 13.9)	2.39 (0.42, 13.5)	2.46 (2.08, 2.92)
	CBD	0	2	17	21	7	0	0.00	0.25 (0.07, 0.92)	2.67 (1.67, 4.28)	4.55 (2.97, 6.95)	3.16 (1.53, 6.52)	0.00	0.86 (0.65, 1.15)
Men	PSP	0	3	17	40	10	0	0.00	0.78 (0.27, 2.30)	3.21 (3.44, 8.83)	18.7 (13.8, 25.5)	11.3 (6.12, 20.7)	0.00	2.64 (2.09, 3.33)
	CBD	0	2	12	7	2	0	0.00	0.52 (0.14, 1.90)	3.89 (2.22, 6.81)	3.28 (1.59, 6.78)	2.25 (0.62, 8.21)	0.00	0.87 (0.58, 1.30)
Women	PSP	0	1	17	35	10	1	0.00	0.25 (0.04, 1.39)	5.18 (3.23, 8.29)	14.1 (10.1, 19.6)	7.53 (4.09, 13.9)	3.41 (0.60, 19.3)	2.29 (1.80, 2.93)
	CBD	0	0	5	14	5	0	0.00	0.00	1.52 (0.65, 3.56)	5.63 (3.35, 9.45)	3.76 (1.61, 8.81)	0.00	0.86 (0.58, 1.28)
Grampian (584,550)														
Total	PSP	0	0	12	9	4	0	0.00	0.00	17.8 (10.2, 31.1)	19.1 (10.1, 36.3)	17.7 (6.87, 45.4)	0.00	4.28 (2.90, 6.31)
	CBD	0	0	3	6	3	0	0.00	0.00	4.45 (1.51, 13.1)	12.7 (5.84, 27.8)	13.3 (4.51, 39.0)	0.00	2.05 (1.17, 3.59)
Men	PSP	0	0	7	4	1	0	0.00	0.00	20.9 (10.1, 43.2)	18.1 (7.03, 46.5)	10.8 (1.90, 61.1)	0.00	4.13 (2.36, 7.22)
	CBD	0	0	1	4	2	0	0.00	0.00	3.00 (0.53, 16.9)	18.1 (7.03, 46.5)	21.6 (5.92, 78.7)	0.00	2.41 (1.17, 4.97)
Women	PSP	0	0	5	5	3	0	0.00	0.00	14.7 (6.29, 34.5)	20.0 (8.54, 46.8)	22.5 (7.64, 66.0)	0.00	4.42 (2.59, 7.57)
	CBD	0	0	2	2	1	0	0.00	0.00	5.89 (1.61, 21.5)	8.00 (2.19, 29.2)	7.48 (1.32, 42.4)	0.00	1.70 (0.73, 3.98)

Age-stratified population denominators for Scotland: 40–49 years = 691,809 (336,136 M/355,673 F); 50–59 years = 791,347 (383,921 M/407,426 F); 60–69 years = 636,719 (308,257 M/328,462 F); 70–79 years = 462,067 (213,396 M/248,671 F); 80–89 years = 221,707 (88,816 M/132,891 F); and ≥90 years = 41,927 (12,620 M/29,307 F) and Grampian: 40–49 years = 77,284 (38,631 M/38,653 F); 50–59 years = 81,920 (40,591 M/41,329 F); 60–69 years = 67,414 (33,442 M/33,972 F); 70–79 years = 47,122 (22,120 M/25,002 F); 80–89 years = 22,630 (9,269 M/13,361 F); and ≥90 years = 4,381 (1,378 M/3,003 F).

Ten prevalent cases (6 PSP, 4 CBS) have undergone post-mortem examination to date. The clinical diagnosis of PSP was confirmed in 5 cases, with CBD identified in the sixth case. In those with CBS, two had CBD, and two had Alzheimer's pathology.

Discussion

This is the first prevalence study of PSP and CBS in Scotland [2]. Due to better case ascertainment, the best estimates come from the regional study, namely 4.28 per 100,000 for PSP, approximately double that of CBS. The lower rates for Scotland nationally are due to under-ascertainment due to fewer methods of ascertainment and less confirmation of the diagnoses due to the larger population size.

Three prevalence studies in PSP in England, conducted in 1999 [8], 2001 [3], and 2016 [9], report prevalence

rates of 6.5 (95% CI 3.8, 10.5) and 4.9 (95% CI 1.8, 10.7) per 100,000 in community level studies, 3.1 (95% CI 2.4, 3.8) and 2.8 (95% CI 2.1, 3.8) per 100,000 in regional level studies, and 1.0 (95% CI 0.9, 1.1) per 100,000 at a national level. The standardized (1996 European population) age-adjusted community level prevalence rates for PSP in the two earlier studies, at 5.0 (95% CI 2.5, 7.5) [3] and 5.0 (95% CI 0.9, 9.2) [8] per 100,000, respectively, are similar to our age-adjusted prevalence, 4.9 per 100,000, standardised to the same 1996 European population. In CBS, only one other age-unrestricted study has been conducted in the UK [9]. The crude prevalence of 2.2 per 100,000 (95% CI 1.6, 3.1) reported in this previous study is similar to the regional crude prevalence rate of 2.1 per 100,000 (95% CI 1.2, 3.6) reported in the current study.

Prevalence rates in the UK are broadly similar to crude prevalence rates reported in other European studies unrestricted by age: 8.3 per 100,000 (95% CI 5.9, 11.3) in the Canton of Geneva, Switzerland [10], and 4.1 (95% CI 0.5,

14.9) and 4.6 (95% CI 0.6, 16.5) per 100,000, both in the Faroe Islands [11, 12]. In contrast, our regional crude prevalence rate is higher than the first, and only, North-American PSP prevalence study which reported a crude prevalence of 1.4 per 100,000 (95% CI 0.7, 2.5) [13]. However, this study was conducted prior to the NINDS-SPSP 1996 international consensus criteria for PSP, and the authors considered they had underestimated prevalence due to their reliance on passive case ascertainment.

Our prevalence rate is similar to one of three identified age-unrestricted Japanese studies, namely the first Yonago City study (5.8 per 100,000, 95% CI 2.5, 11.5) [14]. However, the two other Japanese studies reported significantly higher rates: the later Yonago City study (17.9 per 100,000, 95% CI 11.6, 26.4) [15] and the Koban district study (18.1 per 100,000, 95% CI 9.3, 31.5) [16]. These studies reported rates higher than all other published prevalence studies in PSP. A previous genetic study of the distribution of the tau H1/H2 haplotype in different global populations concluded that the H2 haplotype is probably exclusively Caucasian in origin. Consequently, non-Caucasian populations may have an increased incidence of H1-associated tauopathies since such populations would have nearly twice as many H1 homozygotes [17]. The reported higher prevalence in Japanese studies is therefore of interest, though it should be noted that when only probable diagnoses of PSP are considered in these two Japanese studies, confidence intervals overlap with the remainder of the existing literature. Indeed, inferences regarding geographical differences must be made cautiously as differences in prevalence may reflect differences in incidence, methodology, survival, or other population parameters. While in general incidence studies are therefore usually the preferred approach to study disease causation, they often involve lengthy periods of follow-up and significant resource. It is therefore often more practical to study the prevalence of disease at a particular point in time, though cost-effective alternatives to classic cohort study design for estimating the incidence of rare neurodegenerative diseases in population-based settings have been more recently proposed [18]. Prevalence studies however remain of critical importance as they estimate the burden of disease in a population, which in turn informs priority setting, resource allocation, and the delivery and use of health services.

Outside the UK, four other studies reporting age-unrestricted prevalence rates for CBS have been conducted. In a study in the Canton of Geneva, Switzerland [10], the prevalence of CBS was 3.0 (95% CI 1.6, 5.0) per 100,000, similar to both our study and the study of Coyle-Gilchrist

et al. [9], also conducted in the UK. Our rates are lower compared to studies conducted in Egypt (24.9 [95% CI 3.0, 90.0] per 100,000) [19] and Japan (9.0 [95% CI 3.3, 19.6] per 100,000) [16] and higher than the Faroe Islands (0.0 [95% CI 0.0, 7.6] per 100,000) [12], though confidence intervals overlapped with each of these studies. Overall, therefore, there is not strong evidence to suggest clear geographical or latitudinal differences in the prevalence of PSP or CBS.

Globally, only two previous prevalence studies have sought to determine the prevalence of both PSP and CBS within the same study [9, 10], facilitating an assessment of the relative prevalence of PSP and CBS, independent of variations in methodology, in particular, the methods of case ascertainment or population size. Fleury and colleagues' [10] crude prevalence of PSP was 8.3 per 100,000 (95% CI 5.9, 11.3), nearly three times higher than that of CBS which had a crude prevalence of 3.0 per 100,000 (95% CI 1.6, 5.0), $p = 0.0006$. In contrast, Coyle-Gilchrist and colleagues [9] found the crude prevalence of PSP at 2.8 per 100,000 (95% CI 2.1, 3.8), similar to CBS (2.2 per 100,000, 95% CI 1.6, 3.1), $p = 0.280$. In the present study, at a regional level, our crude point prevalence estimate of PSP was approximately double that of CBS ($p = 0.032$).

Few previous studies have reported either age- or sex-stratified prevalence rates, and no previous study has reported both age- and sex-stratified results. In Fleury and colleagues' [10] study, the peak crude prevalence for both PSP and CBS was in the 80–89-year age group, while in Coyle-Gilchrist and colleagues' [9] study, the peak prevalence for both occurred in the 70–79 age strata. In the study by Osaki and colleagues [16], the peak prevalence for PSP was also in the 80–89-year age group, whereas for CBS, the prevalence was the same across age strata (from 60 to 89 years). What does seem clear across studies is that despite the declared cut-off age of 40 and 50 years in diagnostic criteria for PSP and CBS, these diagnoses are relatively uncommon under the age of 60 years. There is also little existing evidence to suggest clear sex differences in the crude prevalence of PSP or CBS.

Our study has several strengths including the use of active, overlapping methods of case ascertainment with a good proportion examined in person enabling consistent application of diagnostic criteria. In all identified cases, clinicians were contacted 1 year after the prevalence day to ensure all identified individuals had been alive and resident on the prevalence day and had not undergone diagnostic revisions. There are also several limitations which probably mean we have underestimated prevalence. A few people with an alternative diagnosis in the prevalence

period received a revised diagnosis of PSP/CBS after the prevalent period so were excluded. We could not diagnostically verify all cases (either by examination or case note review) to apply possible/probable criteria. Not all GP services sent data (although only two unique cases were identified by GPs). There were few referrals from psychiatry, and few were identified from inpatient mental health discharge diagnostic coding (SMR04). PSP/CBS may be under-recognised in dementia services, and there may also be under-recognition in general neurology and geriatric services. We did not use the capture-recapture method to estimate the completeness of case ascertainment because this method assumes that ascertainment methods are independent, which they were not. GP identification, for example, is largely based on secondary care diagnoses, while SMR01 and SMR04 diagnostic coding is dependent on hospital discharge clinical diagnoses.

In conclusion, the UK prevalence of PSP and CBS has been consistent over recent times. While the new MDS diagnostic criteria [20] for PSP may improve diagnostic sensitivity and allow stratification by phenotype and diagnostic certainty, implementation of these relatively complex criteria in clinical practice will take time.

Acknowledgements

We sincerely thank the many clinicians and PD nurse specialists from across Scotland for their time and effort in notifying us of cases without whose input the study would have been impossible. We also thank Colin McSkimming of the Department of eHealth and NHS Grampian for his assistance with the ECCI searches.

Statement of Ethics

The study protocol was reviewed and approved by the Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP), NHS Scotland, approval number 1718-0245. Written consent was not sought from prevalent cases, as approved by the HSC-PBPP.

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Conflict of Interest Statement

The authors have no conflicts of interest.

Funding Sources

Dr. Swallow received a clinical research fellowship jointly funded by the Chief Scientist Office (CSO) of the Scottish Government and PSP Association.

Author Contributions

D.M.A.S.: study design, data collection and analysis, and first draft and revision of the manuscript; C.E.C.: study conception and design, data collection, and critical review of the manuscript.

Data Availability Statement

Anonymised data relevant to the analyses within this article can be shared at the request of qualified investigators to replicate presented analyses.

Appendix

Scottish Morbidity Record International Classification of Disease Version 10 (ICD-10) Diagnostic Codes Utilised

G23.1: Progressive supranuclear ophthalmoplegia.
G12.22: Progressive Bulbar Palsy code (codes Motor Neuron Disease but known to be misused for PSP) [21]

There is no specific ICD-10 diagnostic code for CBD.

Non-specific coding options explored within ICD-10 for PSP/CBD included “G25.9: Extrapyramidal and movement disorder, unspecified”; “G23.8: Other specified degenerative diseases of basal ganglia”; “G23.9: Degenerative disease of the basal ganglia, unspecified”; “G31.0: Circumscribed brain atrophy”; “G31.8: other specified degenerative diseases of the nervous system”; and “F02.0: Dementia in Pick’s disease.”

READ Codes

F24y0: Progressive supranuclear palsy, F24y2: Steele-Richardson-Olszewski syndrome and F11yz: Other cerebral degeneration.

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