Published in final edited form as:

J Parkinsons Dis. 2020 ; 10(1): 179–184. doi:10.3233/JPD-191744.

Progressive Supranuclear Palsy and Corticobasal Syndrome: A Population-based Study

Cole D. Stang¹, Pierpaolo Turcano, MD¹, Michelle M. Mielke, PhD^{2,†}, Keith A. Josephs, MD¹, James H. Bower, MD¹, J. Eric Ahlskog, PhD, MD¹, Bradley F. Boeve, MD¹, Peter R. Martin^{2,†}, Sudhindra G. Upadhyaya^{2,†}, Rodolfo Savica, MD, PhD^{1,2,*}

¹Mayo Clinic Department of Neurology, Rochester, Minnesota, USA

²Mayo Clinic Department of Health Sciences Research, Rochester, Minnesota, USA

Abstract

Objective: To examine the incidence of and trends in Progressive Supranuclear Palsy (PSP) and Corticobasal Syndrome (CBS) in a population-based cohort of residents of Olmsted County, MN.

Background: Few studies have investigated the incidence of PSP and CBS in the population.

Methods: We used the 1991-2005 population-based cohort study of Parkinsonism in Olmsted County, MN, defined via the Rochester Epidemiology Project. A movement-disorder specialist reviewed medical records to confirm diagnoses of PSP and CBS.

Results: We identified 21 patients with these diagnoses 1991-2005: 18 (85.7%) with PSP, 3 (14.3%) with CBS. The median age at diagnosis was 78 (range: 66-88). 13/21 (62.0%) were male. MRI was performed before diagnosis in 11 patients (8 PSP and 3 CBS); 10 showed atrophy consistent with clinical diagnoses. We observed concordance between clinical and pathological diagnoses in two PSP patients who underwent autopsy. Combined incidence for PSP and CBS in Olmsted County was 3.1 per 100,000 person-years (2.6 per 100,000 person-years, PSP; 0.4 per 100,000 person-years, CBS). Incidence was higher in men (4.5, 95% CI, 2.0-7.0) than women (1.8, 95% CI, 0.5-2.9). A combined, significant trend of increasing incidence was observed between 1991 and 2005 (B=0.69, 95% CI 0.42, 0.96, p<0.001). Median time from symptom onset to death among both groups was 6 years (range PSP, 1-10 years; range CBS, 3-8 years).

Conclusions: The combined incidence for PSP and CBS was 3.1 per 100,000 person-years and higher in men than women. We observed a significant increase in both PSP and CBS, likely due to advancing imaging technology and improved diagnostic ability among physicians.

Introduction

Progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) are neurodegenerative diseases with complex clinical presentations that share clinical features with other forms of Parkinsonism. PSP is clinically characterized by prominent truncal

*Corresponding Author: Rodolfo Savica, MD, PhD, Department of Neurology, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905, (507)284-2120/ Savica.Rodolfo@mayo.edu.

[†]Performed statistical analysis

instability with early falls, parkinsonian features with poor levodopa responsiveness, and vertical supranuclear palsy.¹ CBS typically is characterized by asymmetric apraxia and limb rigidity/dystonia; the Parkinsonism is poorly levodopa-responsive, and alien-limb phenomena may be present.² Both diseases are pathologically characterized by the deposition of an aberrant form of tau protein in the brain tissues.³ However, it should also be noted that CBS pathology may also present similarly to a variety of neurodegenerative conditions ranging from PSP to Alzheimer disease.

Since PSP and CBS are very uncommon, few epidemiological studies have been published. Using the most recent diagnostic criteria, we investigated their incidence in our population-based cohort study of Parkinsonism with onset from 1991 to 2005; we examined sex differences and time-trends. We also described the clinical and neuroimaging characteristics of these patients, survival and, when possible, the pathological findings. Because these diseases share pathological features, we estimated the incidence both separately and combined.

Methods

Cases ascertainment

We used the unique infrastructure of the Rochester Epidemiology Project (REP). Through this medical-records linkage system we identified 669 incident cases of Parkinsonism in Olmsted County, MN from 1991 to 2005.⁴ A movement-disorders specialist (R.S.) reviewed all the clinical records of the 669 patients with Parkinsonism and then the diagnosis of different parkinsonism was given. We reviewed all the cases to confirm the diagnosis of PSP and CBS and updated the diagnoses, if necessary, in concordance with the most recently published diagnostic criteria.^{5, 6} A board-certified neuropathologist reviewed available autopsy reports to confirm the clinical diagnoses when possible. The reliability and validity of case-ascertainment has been reported somewhere else. In summary, to demonstrate the reliability of our case-finding procedure, a second neurologist (J.H.B.) reviewed a number of cases for our original cohort (40 random generated cases). Agreement on presence of parkinsonism or PD was 90.0% (27 out of 30). None of the discrepant cases were PSP or CBS.^{4, 7}

In brief, our diagnostic criteria included two steps: the definition of Parkinsonism as a syndrome and the definition of types of Parkinsonism within the syndrome. Parkinsonism was defined as the presence of at least two of four cardinal signs: rest tremor, bradykinesia, rigidity, and impaired postural reflexes. Among the persons who fulfilled the criteria for Parkinsonism, we applied the diagnostic criteria to classify the type of Parkinsonism.^{5, 6} We identified PSP and CBS separately; however when PSP and CBS were analyzed as a single entity, we referred to them as clinically defined movement disorders-related tauopathies.⁵

Statistical analysis

An incidence rate, for the purpose of this study, is defined as the number of new cases (PSP, CBS) from January 1st 1991 up to December 31st 2005, divided by the number at risk. Typically the denominator takes the form of person-years when the specified period extends

beyond one year or if the duration of observation is unequal for various members of the base population. It should be noted that the populations referred to in our study is the Olmsted county population and the denominator person-years or person-years at risk was extrapolated from the Rochester Epidemiology Project (REP) records-linkage system. More extensive details regarding REP have been reported elsewhere [8]. All incidence rates reported are expressed per 100,000 person- years. No sampling procedures were utilized in our analysis because of direct access to the Olmsted County population. We used survey-weighted linear-regression models specifying year as an independent variable to estimate incidence trends. Kaplan-Meier curves were plotted to model survival time. All statistical analyses were performed using Stata version 13 (StataCorp, College Station, TX) and RStudio version 3.4.2.

Standard Protocol Approvals, Registrations, and Patient Consents

The Mayo Clinic and Olmsted Medical Center Institutional Review Boards approved this study, and participating patients (or their legally authorized representatives) provided informed written consent for use of their medical information for research.⁴ More detailed information about the Olmsted County population is reported elsewhere.⁸⁻¹⁰ Information about the different types of Parkinsonism and clinical and pathological characteristics of this cohort is also reported elsewhere.^{7, 11}

Data Availability Statement

All the relevant data have been shared and published in this article; data regarding case ascertainment of parkinsonism and methodology on case identification have been previously published.⁴

Results

Demographics

Among the 669 incident cases of Parkinsonism in Olmsted County, MN, from 1991 to 2005 we identified 21 cases of clinically defined movement disorders-related tauopathies (PSP or CBS). Of these, 18 (85.7%) received a clinical diagnosis of PSP; 12 (66.7%) were male. Three (14.3%) out of 21 cases were diagnosed with CBS; one was male (33.3%). The median age at the time of symptom onset of PSP and CBS was 74 years (range: 63-87). The median age at diagnosis for these 21 cases was 78 years (range: 66-88 years). The combined overall incidence was 3.1 per 100,000 person-years and was higher in men (4.5, 95% CI, 2.0-7.0) than women (1.7, 95% CI, 0.5-2.9). CBS incidence was 0.4 per 100,000 person-years and PSP incidence was 2.6 per 100,000 person-years. Incidence rates of PSP and CBS from 1991 through 2005 are shown in Figures 1, 2, and 3.

To compare our data with an earlier (non-overlapping) study conducted in the same population (1976-1990),¹² we additionally restricted our population to individuals 50 years or older. We observed an incidence of PSP of 5.0 per 100,000 person-years, which was greater in men (7.6/100,000) compared to women (3.0/100,000); the incidence of CBS in individuals 50 years or older was 0.8 per 100,000 person-years and was similar in men

(0.6/100,000) compared to women (1.0/100,000). When PSP was combined with CBS, the incidence was 5.9 per 100,000 person-years for individuals older than 50 years of age.

Neuroimaging

Of the patients in our cohort, 62% underwent brain imaging studies/MRI. A blinded neurologist reviewed all neuroimaging to assess atrophy. Specifically, 8 (38%) clinically diagnosed PSP patients and all 3 CBS patients had at least one MRI before the clinical diagnosis was made (median: 1 year, range: 1 month - 5 years.); 7/8 PSP patients showed a pattern of atrophy consistent with the clinical diagnosis including midbrain atrophy. Among the 3 CBS patients, more prominent left than right frontal and parietal atrophy was observed.

After the clinical diagnosis was made, 7/18 PSP patients, including 3 who also underwent imaging before, showed midbrain atrophy consistent with the clinical diagnoses.

One PSP patient had no abnormal findings documented at imaging before the clinical diagnosis; however, a repeat MRI after the clinical diagnosis revealed only mild diffused age-related cerebral atrophy. Only one of the three CBS patients had a MRI repeated one year after clinical diagnosis, and occipital lobe atrophy was added to the aforementioned pattern of atrophy.

We observed hypo-metabolism of the frontal lobes and the heads of the caudate nuclei in one PSP patient who underwent a FDG-PET scan before the clinical diagnosis. SPECT scan imaging with F-18 FDG in another PSP patient revealed decreased uptake in the parietal and temporal lobes, left greater than right. One CBS patient who underwent a SPECT scan with Technetium Tc 99m Bicisate showed decreased uptake in left frontal, temporal, and parietal lobes along with the left basal ganglia.

Survival and Post-mortem examinations

The median time from symptom onset to death among PSP patients was 6 years (range: 1-10 years; Figure 4). The median time from symptom onset to death among the 3 CBS patients was also 6 years (range: 3-8 years). Autopsy was performed in 2 PSP patients; they both showed pathological findings consistent with the clinical diagnosis. Specifically, one patient had a pathological diagnosis of PSP, whereas the second had mixed pathological findings showing both tau and alpha-synuclein inclusions.

Discussion

Few epidemiological studies on PSP and CBS have been conducted due to the low prevalence of these diseases and the complexity of the clinical presentation. Using the REP medical records-linkage system, we report an overall incidence for combined PSP and CBS of 3.1 per 100,000 person-years in our population-based cohort between 1991 and 2005. We observed an increased incidence trend during our study period; improved diagnostic criteria and increased knowledge of these rare conditions among physicians—rather than a true increase in the incidence— might explain these results.

The incidence results of these two parkinsonian conditions may be contrasted to recently published Parkinson's disease (PD) incidence findings from the same population. The incidence of PD in Olmsted County for men and women was 17.2 per 100,000 person-years from 1996 to 2005.¹³ This comparison indicates that PD is 6.6 times more frequent than PSP and 43 times more frequent than CBS.

Previous studies examining the incidence of PSP or CBS have provided a wide range from 0.14 to 1.1 per 100,000 person-years.^{12, 14, 15} Reasons for the large differences may be due to the different time periods covered by each study, different methodologies, or different diagnostic criteria. Our study used a large population-based cohort over a 15-year period to update incidence rates for these rare diseases. In a previous study, we reported an incident rate of 0.9 per 100,000 person-years for PSP and 0.2 per 100,000 person-years for CBS, respectively⁴; however, we expanded our cohort to include definite, probable, and possible levels of certainty for the diagnosis of PSP. In addition, the application of the most recent criteria for PSP and CBS led to the identification of a couple of different cases and the exclusion of one previously included case of CBS.

Our results were similar to the most recent incidence of PSP reported in Olmsted County from 1976 to 1990.¹² Although the same population was studied (but in a different time-frame: 1976-1990 vs 1991-2005), small differences in results can be explained by a number of factors. First, we used the most recent diagnostic criteria for PSP,⁵ whereas the previous study did not. Second, there has been increasing recognition of parkinsonism-plus disorders and parkinsonism-subtypes in recent years. Third, longevity has increased, relevant to disorders that surface later in life, such as these tauopathies. However, the clinical characteristics between the two studies were also similar: men have a higher incidence rate than women; the median age of diagnosis was similar, as well as the median survival time of patients diagnosed with PSP. The incidence in a population restricted to individuals over the age of 50 was also similar.

The median survival from the date of symptom onset was found to be 6 years. This is similar to previous studies, which reported a median survival time of 5.3 to 5.9 years from symptom onset.^{12, 16, 17} These relatively short survivals may raise patient concerns until it is recognized that the median age of symptom onset was 74 years.

In our study, we identified 10 patients (7 PSP and 3 CBS) with at least one MRI and 2 patients (1 PSP and 1 CBS) who underwent either a FDG-PET or SPECT before clinical diagnosis. Of these cases, all but one patient showed neuroradiological findings consistent with the clinical diagnoses. Although only two PSP patients underwent autopsy in our cohort, pathological findings were consistent with the clinical diagnoses in both cases. A previous study on discrepancies between the clinical diagnosis of parkinsonism and neuropathological findings in this population-based cohort found a concordance of 52 out of 60 (86.7%) autopsies. Of note, one patient who had a clinical diagnosis of idiopathic Parkinson's disease had a neuropathological diagnosis of PSP. The patient had clinical symptoms of resting tremor, bradykinesia, rigidity and a UPDRS III score of 16.¹¹ Upon autopsy there was the presence of mixed neurodegenerative-vascular disorder, with features

of PSP. The complex clinical presentation and the mixed pathology are in line with the possible discrepancy that at times are seen in clinical-pathology correlation of PSP .

This study has several strengths including its population-based sampling and long follow-up period (15 years). Surveillance bias should not have been an issue, given the population-based study design. Having access to all medical facilities in the area allows us to minimize the effect of this bias on our results. On the other hand, we also acknowledge a number of limitations. First, as in many retrospective-incidence studies, atypical cases may be missed. However, we used the most recent diagnostic criteria to minimize this effect. Moreover, a movement-disorders specialist also reviewed all cases of Parkinsonism to confirm the clinical diagnosis of PSP and CBS. Second, the relative rarity of PSP and CBS translated into small group numbers, despite the population-based design. Thus, the documented clinical parameters may not be truly representative (e.g., onset age, mortality, etc.). Third, we had only a limited number of pathology-proven cases.

In conclusion, our results indicate that among neurodegenerative Parkinsonism disorders, PD is 5.5 times more frequent than PSP and CBS, combined. Although the incidence of PSP and CBS increased from 1991 to 2005 in this population, this likely can be explained by improved technology and diagnostic criteria rather than a true increase in the incidence.

Acknowledgments

Funding/Support: This study was supported by award R01 AG034676 from the National Institute on Aging of the National Institutes of Health and by the Mayo Foundation for Medical Education and Research.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Disclosures

Mr. Stang reports no disclosures.

Dr. Turcano reports no disclosures.

Dr. Mielke receives funding from the National Institutes of Health, and unrestricted research grants from Biogen and Lundbeck. She has consulted for Lysosomal Therapeutics, Inc, and Eli Lilly

Dr. Josephs receives support from NIH grants R01 AG 037491, R01 014942 and R01 NS 089757.

Dr. Bower receives funding from the Parkinson's Disease Foundation, Inc.

Dr. Ahlskog receives royalties from Oxford University Press for three recently published books.

Dr. Boeve receives funding from the National Institute on Aging, the National Institute of Neurological Disorders and Stroke, the Lewy Body Dementia Association, GE Healthcare, Axovant Sciences, Inc., and Biogen.

Mr. Martin reports no disclosures

Mr. Upadhyaya reports no disclosures

Dr. Savica receives funding from the National Institute on Aging, the National Institute of Neurological Disorders and Stroke, and the Parkinson's Disease Foundation, Inc.

Appendix 1:: Authors

Name	Location	Role	Contribution
Cole Stang	Mayo Clinic Neurology	Author	Co-wrote first draft; acquired and interpreted data
Pierpaolo Turcano, MD	Mayo Clinic Neurology	Author	Acquired data; critical revision of manuscript
Michelle M. Mielke, PhD	Mayo Clinic Health Sciences Research	Author	Analyzed data; critical revision of manuscript
Keith A. Josephs, MD	Mayo Clinic Neurology	Author	Acquired and interpreted data; critical revision of manuscript
James Bower, MD	Mayo Clinic Neurology	Author	Acquired and interpreted data; critical revision of manuscript
J. Eric Ahlskog, MD, PhD	Mayo Clinic Neurology	Author	Acquired and interpreted data; critical revision of manuscript
Bradley F. Boeve, MD	Mayo Clinic Neurology	Author	Acquired and interpreted data; critical revision of manuscript
Peter R. Martin	Mayo Clinic Health Sciences Research	Author	Analyzed data; critical revision of manuscript
Sudhindra G. Upadhyaya	Mayo Clinic Health Sciences Research	Author	Analyzed data; critical revision of manuscript
Rodolfo Savica, MD, PhD	Mayo Clinic Neurology and Health Sciences Research	Author	Co-wrote first draft; acquired, interpreted, and analyzed data; supervised study; full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Arena JE, Weigand SD, Whitwell JL, et al. Progressive supranuclear palsy: progression and survival. *Journal of neurology* 2016;263:380–389. [PubMed: 26705121]
2. Parnera JB, Rodriguez RD, Studart Neto A, Nitrini R, Brucki SMD. Corticobasal syndrome: A diagnostic conundrum. *Dement Neuropsychol* 2016;10:267–275. [PubMed: 29213468]
3. Gotz J, Halliday G, Nisbet RM. Molecular Pathogenesis of the Tauopathies. *Annual review of pathology* 2018.
4. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Incidence and pathology of synucleinopathies and tauopathies related to parkinsonism. *JAMA neurology* 2013;70:859–866. [PubMed: 23689920]
5. Hoglinger GU, Respondek G, Stamelou M, et al. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Movement disorders : official journal of the Movement Disorder Society* 2017;32:853–864. [PubMed: 28467028]
6. Armstrong MJ, Litvan I, Lang AE, et al. Criteria for the diagnosis of corticobasal degeneration. *Neurology* 2013;80:496–503. [PubMed: 23359374]
7. Savica R, Grossardt BR, Bower JH, Boeve BF, Ahlskog JE, Rocca WA. Incidence of dementia with Lewy bodies and Parkinson disease dementia. *JAMA Neurol* 2013;70:1396–1402. [PubMed: 24042491]
8. St Sauver JL, Grossardt BR, Yawn BP, Melton LJ, 3rd, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. *American journal of epidemiology* 2011;173:1059–1068. [PubMed: 21430193]
9. St Sauver JL, Grossardt BR, Leibson CL, Yawn BP, Melton LJ, 3rd, Rocca WA. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. *Mayo Clinic proceedings* 2012;87:151–160. [PubMed: 22305027]
10. St Sauver JL, Grossardt BR, Yawn BP, et al. Data resource profile: the Rochester Epidemiology Project (REP) medical records-linkage system. *International journal of epidemiology* 2012;41:1614–1624. [PubMed: 23159830]

11. Turcano P, Mielke MM, Josephs KA, et al. Clinicopathologic discrepancies in a population-based incidence study of parkinsonism in olmsted county: 1991-2010. *Movement disorders : official journal of the Movement Disorder Society* 2017;32:1439–1446. [PubMed: 28843020]
12. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence of progressive supranuclear palsy and multiple system atrophy in Olmsted County, Minnesota, 1976 to 1990. *Neurology* 1997;49:1284–1288. [PubMed: 9371909]
13. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Time Trends in the Incidence of Parkinson Disease. *JAMA neurology* 2016;73:981–989. [PubMed: 27323276]
14. Winter Y, Bezdolnyy Y, Katunina E, et al. Incidence of Parkinson's disease and atypical parkinsonism: Russian population-based study. *Movement disorders : official journal of the Movement Disorder Society* 2010;25:349–356. [PubMed: 20108378]
15. Linder J, Stenlund H, Forsgren L. Incidence of Parkinson's disease and parkinsonism in northern Sweden: a population-based study. *Movement disorders : official journal of the Movement Disorder Society* 2010;25:341–348. [PubMed: 20108376]
16. Maher ER, Lees AJ. The clinical features and natural history of the Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). *Neurology* 1986;36:1005–1008. [PubMed: 3714047]
17. Litvan I, Mangone CA, McKee A, et al. Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study. *Journal of neurology, neurosurgery, and psychiatry* 1996;60:615–620.

Figure 1.
Combined Incidence of PSP and CBS in Olmsted County from 1991-2005

Figure 2.
Incidence of PSP in Olmsted County from 1991-2005

Figure 3.
Incidence of CBS in Olmsted County from 1991-2005

Figure 4.
Kaplan-Meier Survival estimate among PSP Patients in Olmsted County, 1995-2005