Published in final edited form as:

Mov Disord. 2017 December ; 32(12): 1772–1779. doi:10.1002/mds.27198.

Cognitive impairment in progressive supranuclear palsy is associated with tau burden

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Financial Disclosures of all authors

Dr. Koga reports no disclosures.
Dr. Parks reports no disclosures.
Dr. Kasanuki reports no disclosures.
Dr. Sanchez-Contreras reports no disclosures.
Mr. Matthew C. Baker reports no disclosures.
Dr. Josephs receives research support from the NIH (R01-DC010367, R01-DC012519 & R01-AG037491) and the Alzheimer's Association. Dr. Josephs is an editorial board member of *Acta Neuropathologica, Journal of Neurology* and *Parkinsonism and Related Disorders*.
Dr. Ahlskog reports no disclosures.
Dr. Uitti receives research support by the NIH (P50-NS072187, and from Advanced Neuromodulation Systems, Inc./St. Jude Medical, Dr. Uitti is an Associate Editor of Neurology and an editorial board member of Parkinsonism & Related Disorders.
Dr. Graff-Radford reports no disclosures.
Dr. van Gerpen receives research funds from the Mayo Clinic CR program and NIH (P50-NS072187). This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
Dr. Wszolek is partially supported by the NIH/NINDS P50 NS072187, NIH/NIA (primary) and NIH/NINDS (secondary) 1U01AG045390-01A1, Mayo Clinic Center for Regenerative Medicine, Mayo Clinic Center for Individualized Medicine, Mayo Clinic Neuroscience Focused Research Team (Cecilia and Dan Carmichael Family Foundation, and the James C. and Sarah K. Kennedy Fund for Neurodegenerative Disease Research at Mayo Clinic in Florida), the gift from Carl Edward Bolch, Jr., and Susan Bass Bolch, and The Sol Goldman Charitable Trust. Dr. Wszolek serves as Co-Editor-in-Chief of *Parkinsonism and Related Disorders*, Associate Editor of the *European Journal of Neurology*, and on the editorial boards of *Neurologia i Neurochirurgia Polska*, the *Medical Journal of the Rzeszow University*, and *Clinical and Experimental Medical Letters*; holds and has contractual rights for receipt of future royalty payments from patents re: A novel polynucleotide involved in heritable Parkinson's disease; receives royalties from editing *Parkinsonism and Related Disorders* (Elsevier, 2015, 2016) and the *European Journal of Neurology* (Wiley- Blackwell, 2015, 2016).
Dr. Rademakers receives research support from the NIH (P50-NS072187, R01-NS076471 and R01-NS080882).
Dr. Dickson receives support from the NIH (P50-NS072187). Dr. Dickson is an editorial board member of *Acta Neuropathologica, Annals of Neurology*, *Brain*, *Brain Pathology*, and *Neuropathology*, and he is editor in chief of *American Journal of Neurodegenerative Disease*, and *International Journal of Clinical and Experimental Pathology*.

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AP: Conception of the project; Acquisition, analysis and interpretation of data; execution of the statistical analysis; review and edit the draft
KK: Acquisition, analysis and interpretation of data; review and critique
MSC: Acquisition, analysis and interpretation of data;
MB: Acquisition, analysis and interpretation of data;
KAJ: Review and critique; contribution of patients
JEA: Review and critique; contribution of patients
RJU: Review and critique; contribution of patients
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Abstract

Background—Cognitive impairment is one of the core features of progressive supranuclear palsy. This study aimed to clarify the profile of cognitive impairment and its underlying pathology in progressive supranuclear palsy.

Methods—We retrospectively reviewed medical records to evaluate the pattern and severity of cognitive impairment in 121 autopsy-confirmed progressive supranuclear palsy patients. A subset of 37 patients underwent neuropsychological evaluation as part of their clinical work-up. The burden of progressive supranuclear palsy-related tau pathology (neurofibrillary tangles/pretangles, coiled bodies, tufted astrocytes, and threads) was semi-quantitatively scored in 20 vulnerable brain regions. Concurrent pathologies potentially associated with cognitive impairment, such as Alzheimer-type pathology, were also assessed. To evaluate possible genetic risk factors for cognitive impairment, genetic analysis for *APOE* and *MAPT* was performed.

Results—Ninety patients (74%) had documented cognitive impairment based on neurologic evaluation. In a subgroup with neuropsychological testing (N = 37), executive functioning was the most severely impaired cognitive domain. A global cognitive impairment index (Spearman's rho −0.49, P = 0.005) and executive functioning were negatively correlated with total tau burden (Spearman's rho −0.51, P = 0.003), but not correlated with the Alzheimer-type pathology. *APOE* ε4 carriers had more severe amyloid pathology, but total tau burden and overall test battery mean was not different from *APOE* ε4 non-carriers.

Conclusion—Cognitive impairment in progressive supranuclear palsy, most notably executive dysfunction, is associated with severity of progressive supranuclear palsy-related tau pathology.

Keywords

progressive supranuclear palsy; Alzheimer's disease; tau; neuropathology; neuropsychology

Introduction

Progressive supranuclear palsy (PSP) is an atypical parkinsonian disorder associated with supranuclear gaze palsy, postural instability and falls, and cognitive impairment (CI).[1–3] Recently, the Movement Disorders Society criteria for clinical diagnosis of PSP included cognitive dysfunction as one of four core features, which also consist of ocular motor dysfunction, postural instability, and akinesia.[3] Thus, it is increasingly important to obtain a detailed assessment of the clinical features of CI in PSP. CI in PSP helped give rise to the term "subcortical dementia", which is characterized by deficits in attention, processing speed, executive function, and verbal fluency.[4, 5] The largest prospective study has shown that 40–62% of PSP patients developed CI primarily in frontal-executive dysfunction;[6] however, the underlying pathology of CI in PSP still remains unclear.

Pathologic hallmark of PSP is tau accumulation, which can be detected in both neurons and glial cells: neurofibrillary tangles (NFTs), neuropil threads, tufted astrocytes, and coiled bodies.[7, 8] These tau pathologies accompanied by neuronal loss and gliosis affect predominantly the globus pallidus, subthalamic nucleus, substantia nigra, and cerebellar dentate nucleus.[7, 8] Pathological heterogeneity of PSP has been reported, but attempts to correlate this with clinical symptoms have infrequently found definitive correlations.[9–11]

The aim of the present study was to investigate the profile of CI and its underlying pathology in PSP. We hypothesized that the burden of PSP-related tau pathology would correlate with the severity of CI. To address this hypothesis, we retrospectively reviewed medical records and neuropsychological evaluations, semi-quantitatively assessed the burden of tau pathology, and analyzed the correlation between neuropsychological test scores and PSP-related tau burden in autopsy-confirmed PSP. To evaluate possible genetic risk factors for CI in PSP, genetic analysis for *APOE* and *MAPT* was performed.

Materials and Methods

Subjects

All brain tissue samples used in this study were from the Mayo Clinic Brain Bank for Neurodegenerative Diseases. We selected 121 consecutive autopsy-confirmed PSP cases with available medical records that included clinical assessments by a movement disorder specialist at Mayo Clinic between 1998 and 2016. These cases were received from the following sources: CurePSP (58 cases), Udall Center of Excellence for Parkinson's disease (47 cases), Mayo Clinic Alzheimer's Disease (AD) Research Center (13 cases), and State of Florida AD Initiative (3 cases). Some data on these cases have been presented in previous articles.[12, 13] All brain autopsies were performed with the consent of the legal next-of-kin or an individual with power-of-attorney. Studies using these autopsy samples were considered exempt from human subject research by the Mayo Clinic Institutional Review Board.

Clinical Assessment

A neurologist (S.K.) and a psychiatrist (K.K.) abstracted the following information from medical records collected throughout the course of disease as previously conducted:[12–15] demographic information, clinical symptoms, neurological signs, and results from cognitive screening measures and neuropsychological assessments. Clinical phenotypes of PSP (i.e. Richardson syndrome, PSP-corticobasal syndrome (PSP-CBS), PSP-parkinsonism, PSP-frontotemporal dementia, PSP-speech/language disorder, and PSP with predominant cerebellar ataxia) were classified.[3, 12] The determination of the presence of CI was performed in two steps. First, medical records for the main cohort (N = 121) were reviewed for patient symptoms report and diagnostic impressions of the evaluating clinicians for indicators of CI. Examples of these indicators included, but were not limited to "memory loss," "distractibility," "difficulty concentrating," "word finding difficulty," "difficulty with naming," "slowed thinking," "bradyphrenia," "executive dysfunction," "apraxia/dyspraxia," and "visuospatial or perceptual deficits." This review identified 90 patients with suspected CI. Of these patients, test data from a subgroup of 37 patients who underwent neuropsychological assessment at a point in their neurologic work-up were analyzed by a

neuropsychologist (A.P.).[15, 16] Additionally, patients were considered to have depression if a diagnosis of depression was documented and the patient was prescribed an antidepressant medication as a primary treatment for their depressive symptoms. Of the 31 patients not classified as suspected CI, none underwent neuropsychological assessment.

Neuropsychological Assessment

Scores for the following test were available for most patients: Dementia Rating Scale-Second Edition (DRS-2),[17] Wechsler Adult Intelligence Scale (WAIS),[18] Digit Span and Block Design subtests, Trail Making Test (TMT),[19] Wechsler Memory Scale (WMS) Logical Memory,[20] Boston Naming Test,[21] and Semantic Fluency (Animals).[22] Raw test scores were converted to age-corrected standardized scores (T-score, M = 50, SD = 10) based upon procedures using published manuals and widely accepted normative samples.[17, 18, 20, 22] Two indices of global cognitive functioning were obtained: DRS-2 Total score and Overall Test Battery Mean (OTBM). The OTBM was calculated as the average standardized score across all neuropsychological domains (with the exception of the DRS-2 Total score) and is a well-established metric for capturing global cognitive functioning.[23–25] Individual test scores were categorized into five separate cognitive domains: attention/processing speed, executive functioning, episodic memory, language, and visuospatial/construction (see Supplementary Table 1 for the tests that comprise each cognitive domain).

A subset of patients also completed a depression symptom checklist as a part of their neuropsychological assessment, including Beck Depression Inventory,[26] Geriatric Depression Scale,[27] and Patient Health Questionnaire-9.[28] The severity of depression was classified as minimal, mild, moderate, or severe based upon the published scoring procedures for each checklist. Patients who scored in the minimal symptom severity range were classified as patients without depression, whereas patients with clinically significant depressive symptoms in the mild or greater severity range were considered patients with depression.

Neuropathological Assessment: PSP pathology

Immunohistochemistry for phospho-tau (CP13, 1:1000, from Dr. Peter Davies, Feinstein Institute, North Shore Hospital, NY) was used to establish neuropathological diagnosis of PSP.[7] The severity of four tau lesion types, including pretangles/NFTs, coiled bodies, tufted astrocytes, and tau-positive threads, was graded semi-quantitatively on a four-point scale (0, absent; 1, sparse; 2, moderate; 3, frequent)[12] by an experienced neuropathologist (D.W.D), blinded to cognitive data, in 20 brain regions: the temporal cortex, motor cortex, caudate/putamen, globus pallidus, basal nucleus, hypothalamus, ventral thalamus, subthalamic nucleus, thalamic fasciculus, red nucleus, substantia nigra, oculomotor complex, midbrain tectum, locus coeruleus, pontine tegmentum, pontine base, medullary tegmentum, inferior olive, dentate nucleus, and cerebellar white matter (Supplementary Figure 1A). Scores from the hippocampus and amygdala were excluded to remove the influence of Alzheimer-type pathology on the analysis. The regional PSP-related tau burden was defined as the sum of scores for all lesion types in each brain region (range: 0–12). The total PSP-related tau burden was calculated as an average of regional PSP-related tau burden across all 20 brain regions.[29]

To validate the reliability of semi-quantitative assessment of tau burden, we performed quantitative imaging analysis and analyzed the correlation between semi-quantitative and quantitative tau burden. Sections of the motor cortex from 114 PSP cases (sections were unavailable in 7 cases) were scanned on the ScanScopeXT (Aperio Technologies, Vista, CA). The grey matter was annotated using ImageScope-11.2 (Aperio Technologies) and analyzed in Spectrum-11.2 (Aperio Technologies) using a custom-designed color deconvolution algorithm to detect only CP13-positive pathology (Supplementary Figure 1B).[30] Total tau burden was expressed as a percent ratio of the area of immunoreactive pixels to the total area of the annotated region. The Spearman rank correlation test showed strong correlation between semi-quantitative and quantitative tau burden (Spearman's rho 0.86, $P = 2 \times 10^{-7}$) (Supplementary Figure 1C).

Neuropathological Assessment: concurrent pathology

A Braak NFT stage and Thal amyloid phase were assigned to each case with thioflavin S fluorescent microscopy.[31, 32] Numbers of senile plaques and NFTs are counted in nine brain regions: mid-frontal, superior temporal, inferior parietal, motor cortex, visual cortex, endplate, CA2/3, CA1, and subiculum. Neuropathological diagnosis of AD was based on the consensus criteria for the neuropathologic diagnosis of AD.[33] In this study, both high and intermediate likelihood cases were diagnosed with AD. Neuropathological diagnosis of argyrophilic grain disease, Lewy-related pathology, hippocampal sclerosis and cerebrovascular pathology were established previously described.[13] TDP-43 pathology was not included in this study because our previous study showed that TDP-43 pathology was present in 7% of PSP, but it was not associated with CI.[13]

Genetic Analysis

We performed genetic analysis in cases with available frozen brain tissue (N = 118). For genotyping, genomic DNA was extracted from cerebellum of frozen brain tissue using standard procedures. Genotyping for *APOE* alleles (SNP rs429358 C/T and rs7412 C/T) and *MAPT* H1/H2 (SNP rs1052553 A/G, A = H1, G = H2) was assessed with TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA) as previously reported.[12] Genotype calls were obtained with SDS v2.2.2 software (Applied Biosystems).

Statistical Analysis

All statistical analyses were performed in SigmaPlot 12.3 (Systat Software, San Jose, CA) and SPSS Statistics 19 (IBM, Chicago, IL). A chi-square or Fisher's exact test was performed for group comparisons of categorical data as appropriate. Mann-Whitney rank sum test or t-test was used for group comparison analysis of continuous variables as appropriate. The Spearman rank correlation test was used to assess the correlation between each test score or demographic information and PSP-related tau burden. Bonferroni corrections were utilized to adjust for multiple testing separately for some analyses. Significance levels for P values were mentioned in each Table or Figure legend. Hierarchical regressions were conducted to determine whether total tau burden predicted neuropsychological performance after controlling for co-variates.

Results

Comparison between PSP with and without CI

The total cohort included 121 patients with autopsy-confirmed PSP. Of those, 90 (74%) patients were documented with CI based on the record review. The frequencies of CI in each clinical phenotype were 75% in Richardson syndrome (67/89), 57% in PSP-CBS (8/14) and PSP-parkinsonism (4/7), 100% in PSP-frontotemporal dementia (4/4), PSP-speech/language (1/1), and PSP with predominant cerebellar ataxia (1/1), and 80% in unclassified cases because of insufficient clinical information (4/5). Table 1 compares the demographic information and pathologic features between PSP with CI (PSP-CI) and PSP without CI (PSP-NC). The age at onset and death, disease duration, sex ratio, frequency of family history of dementia and parkinsonism, and frequency of clinical diagnosis of PSP did not differ between groups. Of note, depression was more frequently seen in PSP-CI than in PSP-NC (59% vs 35%, P = 0.04). Although the average brain weight was less in PSP-CI than in PSP-NC, other neuropathological features, including Braak neurofibrillary tangle stage, Thal amyloid phase, and frequency of concurrent pathologies of dementia were not different between the two groups.

To address the hypothesis that PSP-related tau affects frequency and severity of CI, we compared total tau burden and regional tau burden between PSP-CI and PSP-NC. Total tau burden (Table 1) and regional tau burden in the pontine base and cerebella white matter (Supplementary Figure 2) were significantly higher in PSP-CI than in PSP-NC. In contrast, the number of senile plaques and NFTs in nine brain regions were not significantly different between the two groups (Supplementary Figure 2). These results suggest that PSP-related tau burden, but not concurrent pathologies of dementia, is associated with CI in PSP.

Profile of CI in PSP

To characterize the profile and severity of CI, we analyzed neuropsychological records of 37 patients (57% men, 97% Caucasian). Table 2 shows demographic information and results of neuropsychological tests. For the two global CI indices, the DRS-2 Total Score was more impaired relative to the OTBM. The most impaired domain was executive functioning, although none of the cognitive domain mean scores fell within the clinically impaired range (i.e., 1.5 SD below the mean, T-score < 35). Length of disease duration and duration of interval between testing and death were not significantly correlated with any of the global cognitive index or domain mean scores. Neither the OTBM nor the domain mean scores were significantly different when compared among the PSP clinical phenotypes (Supplementary Table 2).

Twenty-six of the 37 patients were classified as having depression based on a depression screening instrument given at the time of their neuropsychological assessment. Of those, 12 patients (46%) reported clinically significant depressive symptoms. Group difference analysis indicated that there was no significant difference in cognition between patients with and without depression (OTBM: 42 ± 8 vs 40 ± 8, P = 0.88).

Total tau burden negatively correlates with neuropsychological performance

To elucidate the association between tau burden and severity of CI, we performed Spearman correlation analysis between each neuropsychological test and total tau burden (Table 2). The OTBM was negatively correlated with total tau burden (Spearman's rho −0.49, P = 0.005), but not with the number of senile plaques (Spearman's rho 0.03, P = 0.87) or NFTs (Spearman's rho −0.09, P = 0.62) (Figure 1). These results suggest that PSP-related tau pathology is associated with the severity of CI in PSP, but Alzheimer-type pathology is not.

Next, we examined the extent to which each cognitive domain and neuropsychological test score was correlated with total tau burden (Table 2). Deficits in executive functioning (Spearman's rho −0.51, P = 0.003) were negatively correlated with the total tau burden. Conversely, Visuospatial/Construction was not significantly correlated with total tau burden. Tau burden in some specific regions were negatively correlated with executive functioning (e.g. motor cortex: Spearman's rho −0.51, P = 0.005; globus pallidus: Spearman's rho −0.52, P = 0.004), but these were not statistically significant after Bonferroni corrections.

Hierarchical regressions were conducted to determine the contribution that total tau burden predicted CI after controlling for age at testing, age at death, and disease duration (Supplementary Table 3). The first regression included age at testing, age at death, and disease duration in the first model; the second model added total tau burden to determine its contribution to OTBM considering the covariates. The first model accounted for 9.8% of the total variance in OTBM, but was not statistically significant. The second model was statistically significant and accounted for 24.3% of OTBM variance [F (1, 27) = 6.381, P = 0.018]. Of all the variables in the second model, only total tau burden ($\beta = -0.524$, P = 0.018) was a statistically significant predictor. The second regression included the age and disease duration variables as in the first regression, but the executive functioning domain mean score was used as the dependent variable. The final model included total tau burden and accounted for 31.8% of the total variance in executive functioning [F (3, 28) = 4.607, P = 0.006]. The change in R^2 of .236 was statistically significant [FΔ (1, 28) = 10.723, P = 0.003]. No other neuropsychological domain means were significantly predicted from the age variables, disease duration, or total tau burden.

PSP with coexisting AD

We have shown that Alzheimer-type pathology was not related to the presence or severity of CI in PSP. To further support this finding, we compared pathological and clinical features between PSP with AD (PSP/AD) and PSP. As shown in Table 1, 15 out of 121 patients had a concurrent pathological diagnosis of AD. As expected, age at death, Braak neurofibrillary tangle stage and Thal amyloid phase were higher in patients with PSP/AD (Table 3). Interestingly, PSP/AD had lower total tau burden compared to PSP, although the frequency of CI absent of neuropsychological test data was not different between the two groups. Of the 37 patients with neuropsychological data, six patients were PSP/AD. The OTBM was not statistically different between PSP and PSP/AD, which is consistent with the finding that Alzheimer-type pathology did not correlate with the severity of CI. Taken together, coexisting AD did not significantly impact the frequency or severity of CI in PSP.

Genetic analysis

Genetic analysis revealed no significant difference for either *APOE* ε4 frequency or *MAPT* H1/H1 genotype between PSP-CI and PSP-NC. Compared to *APOE* ε4 non-carriers, *APOE* ε4 carriers had higher Thal amyloid phase, but unexpectedly, the frequency of CI was lower in *APOE* ε4 carriers (Table 4). The OTBM and total tau burden were not different between the two groups (Table 4). These results suggest that *APOE* ε4 allele does not associate with CI in PSP, although it is associated with more severe amyloid pathology. *MAPT* is a gene of interest because *MAPT* H1/H1 genotype is a risk factor of PSP; however, there were no difference in clinical and pathological features between H1/H1and H1/H2 genotype (Table 4). The association between genotype and regional tau burden was also analyzed, but there was no significant difference in any regional tau burden between ApoE genotypes or MAPT haplotypes.

Discussion

The main findings of this retrospective clinicopathological study are (1) at least 74% of PSP patients had CI, primarily in executive functioning and (2) the total PSP-related tau burden, but not Alzheimer-type pathology, correlated with severity of CI in PSP. The first finding supports evidence from the literature that were mostly based on clinically-diagnosed PSP patients.[5, 6] Our second finding is the first pathological evidence that PSP-related tau pathology is associated with cognitive function in PSP.

The results of our study support previous studies on the profile of CI in PSP; multiple cognitive domains are affected, especially executive function.[5, 6] We also analyzed the possible influence of depression on CI, since patients with depression are often thought to “masquerade” as CI involving primarily slowed processing speed and inattention due to the depressive symptoms.[34, 35] Depression was more frequently seen in PSP-CI compared to PSP-NC; however, when a subset of patients with self-reported depression was compared, no differences in test data were identified. These results suggest that CI in PSP is less affected by psychopathology, such as depression, which is consistent with a previous investigation.[36] Nevertheless, it is worth noting that about half of the patients in our PSP cohort had depression. Although the reported frequency of depression in PSP varies 18% to 42%,[37, 38] our results suggest that depression may be more common than previously thought; therefore, it is important to assess depressive symptoms in PSP, and if CI is suspected, a thorough objective cognitive evaluation may be necessary to better determine the relationship between depression and cognition.

Pathological analysis confirmed our hypothesis that burden of PSP-related-tau pathology would correlate with the severity of CI in PSP. Total tau burden and regional tau burden in two brain regions (i.e. pontine base, and cerebellar white matter) were significantly higher in PSP-CI than in PSP-NC. Moreover, total tau burden significantly predicted neuropsychological functioning (OTBM and executive functioning) after accounting for age at testing, age at death, and disease duration. Nevertheless, the regions responsible for CI in PSP remain ambiguous. Regional tau burden was nominally higher in several brain regions, but the differences were not statistically significant. We assume that the total tau burden may reflect overall disease severity and that PSP patients in more advanced stages exhibit more

severe CI. This is consistent with a previous study that showed CI was related to disease severity whether measured by Clinician Global Impression, Hoehn and Yahr stage, or motor disability.[6] As hypothesized by Fiorenzato et al., who examined CI in multiple system atrophy, pathology in circuits between cortical and subcortical regions would affect cognitive functioning rather than in a specific region.[39]

To examine whether concurrent pathologies affect CI in PSP, we compared clinical and pathological features between PSP/AD and PSP. Although the number of patients with PSP/AD was small and Alzheimer-type pathology was relatively mild, we found no significant difference in frequency and severity of CI in PSP compared to PSP/AD. This is consistent with literature reporting CI in corticobasal degeneration; 59% of corticobasal degeneration had Alzheimer-type pathology, but it had minimal effect on the rate of dementia progression and dementia duration.[40] Although it remains inconclusive, there was not enough evidence to suggest that Alzheimer-type pathology affected cognition in PSP-CI.

Genetic analysis for *APOE* also supported the idea that Alzheimer-type pathology was not associated with CI in PSP. *APOE* ε4 allele is the strongest genetic risk factor of AD.[41] *APOE* has an important role in Aβ metabolism, Aβ deposition in senile plaques, and amyloid angiopathy.[42, 43] In our study, *APOE* ε4 carriers had more severe amyloid pathology than non-carriers; however, unexpectedly, the frequency of CI was lower in ε4 carriers. Although the reason of low frequency of CI in ε4 carriers was unclear, given the total tau burden was not different, this different frequency of CI might be fortuitous due to the small size. This result suggests that Alzheimer-type pathology driven by *APOE* ε4 does not increase the frequency of CI in PSP.

A limitation of our study is its retrospective nature and the fact that only a subset of patients (41% with CI) had formal neuropsychological assessment. Furthermore, due to the retrospective nature of this study, the evaluations were performed in the clinical context between multiple clinicians. Also, because assessment of CI in the main cohort was based on physician's impression and patients' subjective complaints documented in medical records, the number of PSP patients with CI may be underestimated. Only six patients had PSP/AD in the subgroup; therefore, the detection of different patterns of CI between patients with and without AD was under-powered. Another limitation is that motor symptoms in PSP may cloud the interpretation of cognitive tests, especially with tests that tend to rely on motor speed (i.e., processing speed), as bradykinesia is one of the most frequent motor signs in PSP.[16, 44] Cognitive tests relying less on motor-dependent tests should be prioritized to overcome this potential confound. Also, the presence of executive dysfunction could impact learning efficiency in some patients thus attenuating delayed episodic memory scores. The impact of this effect on overall memory performance was unaccounted for in our study. Finally, some brain regions that are typically considered to be related to CI (i.e. the frontal and parietal lobe, hippocampus, and amygdala) were not assessed in diagnostic semi-quantitative assessment of tau pathology in PSP. Given that these data independently collected from the current study, the data shown here were completely unbiased in this sense. A final strength of our study is that the diagnoses of PSP were pathologically confirmed, while most of the existing literature on CI in PSP is based on clinical diagnosis.

Concluding, the results of our study showed that a majority of PSP patients developed CI, primarily involving executive functioning, and that PSP-related tau burden, rather than Alzheimer-type pathology, was correlated with the severity of CI. A comprehensive neuropsychological evaluation may be helpful for identifying CI in patients with PSP as well as assisting in establishing a clinical diagnosis of PSP based on the pattern of CI and the presence or absence of executive dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank the patients and their families who donated brains to help further the scientific understanding of neurodegeneration. The authors would also like to acknowledge Linda Rousseau and Virginia Phillips (Mayo Clinic, Jacksonville) for histologic support, Monica Castanedes-Casey (Mayo Clinic, Jacksonville) for immunohistochemistry support, Drs. William P. Cheshire, Kevin B. Boylan (Mayo Clinic, Jacksonville), Erika Driver-Dunckley (Mayo Clinic, Scottsdale), and David S. Knopman (Mayo Clinic, Rochester) for contributing patients, and Drs. Jane Cerhan, Robert Ivnik, Mary Machulda, Jeff Smigielski, Glenn Smith, Max Trenerry (Mayo Clinic, Rochester), Tanis Ferman, John Lucas, Otto Pedraza, Beth Rush, Mark Schwartz (Mayo Clinic, Jacksonville), and Dona Locke (Mayo Clinic, Scottsdale) for neuropsychological testing.

Funding

This work is supported by NIH grants P50 NS072187 and R35 NS097261 and a Jaye F. and Betty F. Dyer Foundation Fellowship in progressive supranuclear palsy research.

List of abbreviations

CI	cognitive impairment
DRS	Dementia Rating Scale
OTBM	overall test battery mean
PSP	progressive supranuclear palsy
PSP/AD	PSP with coexisting Alzheimer’s disease
PSP-CI	PSP with CI
PSP-NC	PSP without CI
TMT	Trail Making Test
WAIS	Wechsler Adult Intelligence Scale
WMS	Wechsler Memory Scale.

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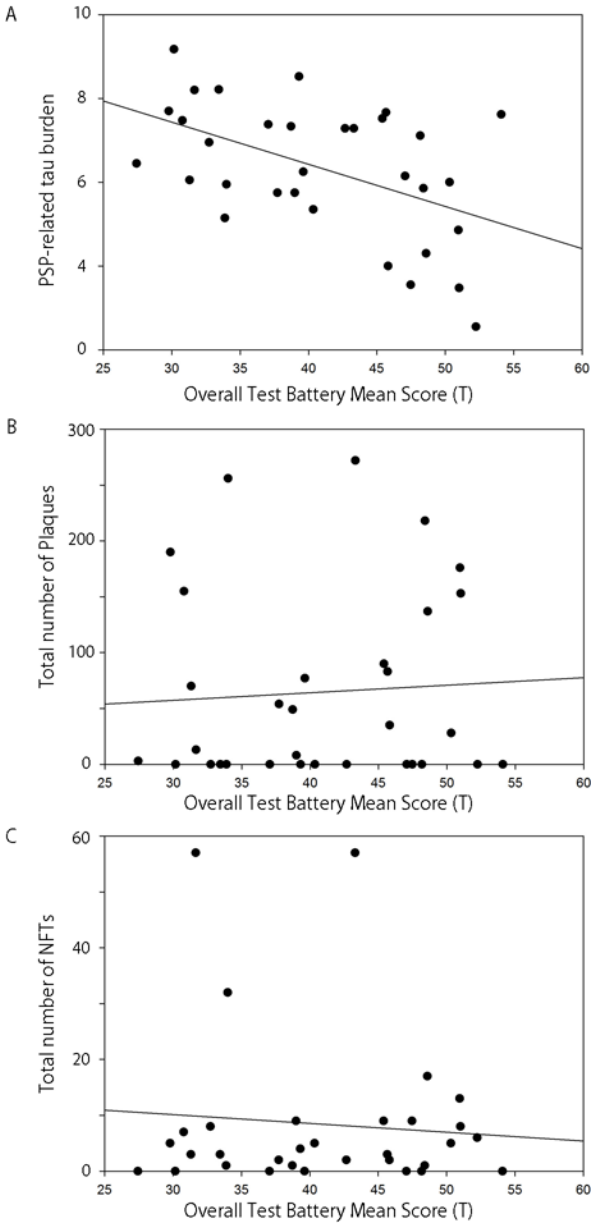

Figure 1.

Spearman correlation analyses show that overall test battery mean score is negatively correlated with PSP-related tau burden (A, Spearman's rho −0.49, P = 0.005), but not with the number of senile plaques (B, Spearman's rho 0.03, P = 0.87) or neurofibrillary tangles (C, Spearman's rho −0.09, P = 0.62).

Table 1

Comparison of demographic, clinical, and pathologic features between PSP-CI and PSP-NC

Features	Total (N = 121)	PSP-CI (N = 90)	PSP-NC (N = 31)	P value
Male, No. (%)	74 (61%)	55 (61%)	19 (61%)	0.85
Age at onset, years	66 ± 8	66 ± 8	66 ± 9	0.74
Age at death, years	74 ± 8	74 ± 8	74 ± 9	0.98
Disease duration, years	7 (5, 9)	7 (5, 9)	7 (5, 12)	0.73
Family history of dementia	28 (23%)	23 (26%)	5 (16%)	0.41
Family history of Parkinsonism	21 (17%)	16 (18%)	6 (19%)	0.94
Having clinical diagnosis of PSP	91 (75%)	70 (78%)	21 (68%)	0.38
Pathology				
Brain weight, grams	1180 ± 140	1160 ± 140	1230 ± 150	0.02
Braak NFT stage	II (II, III)	II (II, III)	II (II, III)	0.59
Thal amyloid phase	0 (0, 3)	0 (0, 3)	1 (0, 3)	0.20
Alzheimer's disease	15 (12%)	9 (10%)	6 (19%)	1.00
Argyrophilic grain disease	31 (26%)	23 (26%)	8 (26%)	1.00
Hippocampal sclerosis	1 (1%)	1 (1%)	0 (0%)	1.00
Cerebrovascular pathology	14 (12%)	10 (11%)	4 (13%)	1.00
Lewy-related pathology	9 (7%)	8 (9%)	1 (3%)	1.00
Total tau burden	6 (4, 8)	6 (5, 8)	6 (4, 8)	<0.001

Values are n (%), mean ± SD, and median (25^{th}, 75^{th} %-tile). Abbreviations: NFT, neurofibrillary tangle; PSP-CI, progressive supranuclear palsy with cognitive impairment; PSP-NC, progressive supranuclear palsy without cognitive impairment.

Table 2

Relationship between neuropsychological variables and total tau burden

Features	N	PSP	Spearman's rho	P value
Age at Testing, years	37	71 ± 8	−0.49	0.002
Age at Disease Onset, years	36	67 ± 8	−0.49	0.008
Age at Death, years	37	75 ± 8	−0.44	0.006
Education Level, years	37	15 ± 3	−0.12	0.49
Global Cognitive Functioning				
Overall Test Battery Mean	32	40 (34, 48)	−0.49	0.005*
DRS-2 Total Score	33	33 (23, 47)	−0.47	0.006*
Attention/Processing Speed	32	45 (37, 49)	−0.42	0.02
Executive Functioning	32	37 (28, 46)	−0.51	0.003*
Episodic Memory	32	44 (35, 54)	−0.46	0.008
Language	32	43 (37, 47)	−0.31	0.09
Visuospatial/Construction	32	43 (35, 47)	−0.033	0.86

All test scores are shown as standardized age-corrected T-scores (M = 50, SD = 10). Spearman's rho is calculated as a correlation between each score and total tau burden.

*indicates statistical significance after applying a Bonferroni correction for multiple testing in neuropsychological scores (P < 0.0071).

Table 3

Clinical and pathological features compared between PSP/AD and PSP

Features	PSP/AD	PSP	P value
Main cohort	**N = 15**	**N = 106**	
Disease duration, years	9 (6, 13)	7 (5, 9)	0.10
Age at death, years	81 ± 6	73 ± 8	<0.001
Braak neurofibrillary tangle stage	IV (IV, V)	II (I, III)	<0.001
Thal amyloid phase	4 (3, 4)	0 (0, 2)	<0.001
Total tau burden	1.4 ± 0.4	1.6 ± 0.3	0.03
Cognitive impairment	9 (60%)	81 (76%)	1.00
Subgroup patients	**N = 6**	**N = 31**	
Disease duration	8 (6, 10)	7 (5, 9)	0.62
Age at death	79 ± 7	74 ± 7	0.13
Braak neurofibrillary tangle stage	IV (IV, V)	II (II, III)	<0.001
Thal amyloid phase	4 (3, 4)	0 (0, 3)	<0.001
Total tau burden	1.5 ± 0.4	1.6 ± 0.4	0.47
Overall Test Battery Mean	43 (32, 51)	40 (33, 47)	0.72
Attention/Processing Speed	47 (35, 48)	44 (37, 50)	0.84
Executive Functioning	46 (26, 47)	37 (28, 45)	0.88
Episodic Memory	32 (28, 59)	46 (35, 54)	0.48
Language	42 (35, 51)	43 (36, 47)	1.00
Visuospatial/Construction	44 (35, 48)	43 (35, 47)	0.98

Overall Test Battery Mean and domain mean score are available for 5 patients in PSP/AD and 27 patients in PSP. Abbreviation: PSP, progressive supranuclear palsy; PSP/AD, PSP with Alzheimer's disease.

Table 4

Cognitive and pathological features in each *APOE4* or *MAPT* haplotype

Features	*APOE4* + (N = 28)	*APOE4* − (N = 90)	P value	*MAPT* H1/H1 (N = 103)	*MAPT* H1/H2 (N = 15)	P value
Male, No. (%)	19 (68%)	53 (59%)	0.53	61 (59%)	11 (73%)	0.45
Age at death, years	73 ± 9	74 ± 8	0.66	73 ± 9	74 ± 8	0.66
Cognitive impairment	14 (56%)	74 (80%)	0.002	76 (74%)	12 (80%)	1.00
Overall Test Battery Mean	41 ± 9	41 ± 8	0.89	40 ± 8	44 ± 8	0.24
Braak neurofibrillary tangle stage	III (II, III)	II (II, III)	0.61	II (II, III)	II (II, IV)	0.68
Thal amyloid phase	3 (1, 4)	0 (0, 3)	<0.001	0 (0, 3)	1 (0, 3)	0.71
Alzheimer's disease	6 (21%)	9 (10%)	1.00	12 (12%)	3 (20%)	1.00
Lewy-related pathology	0 (0%)	8 (9%)	1.00	4 (4%)	4 (27%)	1.00
Total tau burden	7 (6, 7)	7 (4, 8)	0.93	7 (6, 7)	7 (4, 8)	0.93

Values are n (%), mean ± SD, and median (25th, 75th %-tile).