

First description of the clinical and neuroimaging trajectory in presymptomatic Progressive supranuclear palsy

Authors: Jesús García Castro¹, Lúdia Vaqué-Alcázar¹, Sara Rubio-Guerra¹, Judit Selma-González¹, Alejandra O. Morcillo-Nieto¹, Maria Franquesa-Mullerat¹, Oriol Dols-Icardo¹, Alexandre Bejanin¹, Olivia Belbin¹, Juan Fortea¹, Daniel Alcolea¹, Maria Carmona-Iragui¹, Carla Abdelnour¹, Isabel Barroeta¹, Miguel Santos-Santos¹, M. Belén Sánchez-Saudinós¹, Isabel Sala¹, Alberto Lleó¹, Ignacio Illán-Gala¹.

1. Sant Pau Memory Unit, Department of Neurology, IR SANT PAU, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

BACKGROUND

Progressive supranuclear palsy (PSP) is classically described as a rapidly progressive motor syndrome. However, these canonical clinical features reflect advanced disease stages. There is therefore an urgent need for robust biomarkers capable of identifying PSP in its earliest phases, when subtle cognitive, language, or behavioral changes first emerge and disease-modifying interventions are most likely to be effective. Here, we demonstrate that MRI-derived models can predict underlying PSP pathology years before the onset of overt clinical symptoms.

METHODS

We identified autopsy-confirmed PSP cases from ADNI and NACC who were cognitively normal at baseline and had at least one MRI. Demographic, clinical, and neuropsychological data were reviewed. Cortical, subcortical, and brainstem metrics were extracted with FreeSurfer. We used a multinomial logistic regression model (MLRM) based on MRI-derived cortical and subcortical measures to estimate the probability of PSP pathology¹. Then, we applied a data-driven MRI signature combining brainstem and frontotemporal metrics to track disease progression².

Subject	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Thal phase	3	2	3	3	3
Braak phase	5	3	3	2	3
CERAD score	2	1	2	0	1
ADNC	2	1	2	1	2
Vascular pathology	Present	Present	NA	NA	NA
CAA	Moderate	Mild	NA	NA	NA
Lewy	None	None	None	Olfactory bulb	None
Hippocampal sclerosis	None	None	NA	NA	NA
FTLD-tau	PSP	PSP	PSP	PSP	PSP
FTLD-TDP-43	None	None	LATE Stage 2	None	None

Table 1

REFERENCES

1 Illán-Gala I, Nigro S, VandeVrede L, et al. Diagnostic Accuracy of Magnetic Resonance Imaging Measures of Brain Atrophy Across the Spectrum of Progressive Supranuclear Palsy and Corticobasal Degeneration. JAMA Netw Open. 2022;5(4):e229588. Published 2022 Apr 1. doi:10.1001/jamanetworkopen.2022.9588
2 García-Castro J, VandeVrede L, Donohue MC, et al. Potential role of MRI to optimize clinical trial design for progressive supranuclear palsy and corticobasal degeneration. J Prev Alzheimers Dis. 2026;13(3):100486. doi:10.1016/j.tjpad.2026.100486

RESULTS

Five participants had PSP neuropathology. The MLRM identified PSP as the most probable pathology in all five using scans acquired a mean of 9.6 years before death. Sensitivity at first MRI was 60%, reaching 100% 8.7 years before death. At the first scan classified as PSP, no participant had Richardson’s syndrome or probable PSP, and all were cognitively unimpaired. During follow-up, three participants developed cognitive impairment; two received a final diagnosis of Alzheimer’s disease and one of unspecified dementia. Longitudinal MRI was available in three participants and showed a mean 15% decline in the PSP MRI signature. Among cognitively normal ADNI controls without recorded PSP pathology, the model yielded false-positive predictions in 33% at baseline. This finding requires caution because early PSP pathology is not systematically recorded in ADNI.

CONCLUSION

PSP-related neurodegeneration may be detectable with neuroimaging years before clinical manifestations, supporting screening of healthy-aging cohorts and prevention-study design. Future work should assess specificity in autopsy cohorts that systematically record early PSP pathology.

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Cohort	NACC	NACC	ADNI	ADNI	ADNI
Sex	Female	Female	Male	Female	Female
Age at first visit	75	77	70	82	78
Age at death	87	93	80	84	92
First clinical diagnosis	Not CI	Not CI	Not CI	Not CI	Not CI
Last clinical diagnosis	AD	AD	Dementia	Not CI	Not CI
First CDR-GLOB	0.5	0	0	0	0
Last CDR-GLOB	2	0	0.5	0.5	0
First CDR-SUM	1	0	0	0.5	0
Last CDR-SUM	11	0	4	1	0
First MMSE	26	30	28	27	30
Last MMSE	3	30	20	23	26

Table 2

