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Biomarker-Based Corticobasal Syndrome Classification: The Added Value of Deep Phenotyping and Population Diversity

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We read with great interest the article by Palleis and colleagues,[1] which prospectively stratified 50 patients with corticobasal syndrome (CBS) using cerebrospinal fluid (CSF)/amyloid-positron emission tomography (PET) (Aβ), tau-PET, and CSF α-synuclein (αSyn) seed amplification assays (SAA), relating these biomarker profiles to both cross-sectional and longitudinal clinical features. The authors are to be commended for their comprehensive, multimodal biomarker approach and for elucidating the molecular heterogeneity underlying CBS.

As the authors note, the presence of biomarkers in older individuals does not necessarily indicate that they are the primary drivers of the CBS phenotype. We were, however, intrigued by the finding that Aβ+ patients were significantly older than Aβ− patients. Particularly, CBS with underlying Alzheimer's disease (AD) pathology typically manifests in younger-onset AD and affects younger patients than CBS due to corticobasal degeneration and CBS-predominant variant of progressive supranuclear palsy (PSP).[2] We inquire whether Aβ positivity in this cohort primarily reflects age-related co-pathology rather than primary AD neuropathological changes. This finding aligns with αSyn-SAA positivity, which also correlates with AD biomarkers. Additionally, in the Palleis et al. sample, tau-predominant patients were the younger subgroup (ie, less likely to have age-related co-pathology), and regardless of the biomarker used for patient stratification, those with one or more positive biomarkers were older than those with none.

Beyond its focus on biomarkers, this study would also help identify key clinical features that remain highly informative for assessing the likelihood of an underlying 4R-tauopathy versus AD or Lewy-type synucleinopathy (LTS). Those include the presence of oculomotor dysfunction,[3] hyposmia/anosmia, rapid eye movement sleep behavioral disorder, and visual hallucinations.[4,5] The authors reported the subscores of the PSP-Rating Scale data stratified by biomarker positivity in Figure S4, although no inferential statistics were used for hypothesis-driven analysis. In Figures S4 to S6, we can see that the ocular motor dysfunction subscore was higher in the tau+ subgroup than in the tau– subgroup, whereas visual hallucinations were twice as frequent in patients stratified as LTS + AD than in those stratified as AD only. We consider that adding these clinical aspects is meaningful for interpreting those cases' biomarker profiles, as it would illustrate both the utility and the challenges of future application of this stratification in clinical practice. This would allow not only leveraging the deep clinical phenotyping of prospective cohorts such as the Munich cohort[1] but also integrating it with initiatives across the world spanning diverse PSP populations.[6,7]

Relatedly, when uncertainty exists regarding primary versus co-pathology, FDG (fluorodeoxyglucose)-PET patterns can provide complementary information on neurodegenerative topography and may be particularly useful alongside amyloid biomarkers, as previously demonstrated for differentiating AD-related CBS from non-AD CBS.[5] We therefore support the integration of combined biomarker strategies (Aβ biomarkers, FDG-PET, and SAA) in ambiguous cases.

Overall, the study provides compelling evidence that biomarker profiles correspond to clinically relevant differences, including greater cognitive impairment in Aβ-positive cases and milder motor progression in αSyn-positive patients. We believe that incorporating deep phenotyping data for each subgroup would further enhance the interpretability and translational applicability of this critical biomarker-based CBS framework.

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References

1. Palleis C, Bernhardt AM, Weidinger E, et al. A biomarker-based classification of corticobasal syndrome. Mov Disord 2025;41(1):129–142. https://doi.org/10.1002/mds.70070
2. Koga S, Josephs KA, Aiba I, Yoshida M, Dickson DW. Neuropathology and emerging biomarkers in corticobasal syndrome. J Neurol Neurosurg Psychiatry 2022;93(9):919–929. https://doi.org/10.1136/jnnp-2021-328586
3. Parmera JB, de Godoi Carneiro C, de Almeida IJ, et al. Probable 4-repeat tauopathy criteria predict brain amyloid negativity, distinct clinical features, and FDG-PET/MRI Neurodegeneneration patterns in corticobasal syndrome. Mov Disord Clin Pract 2024;11(3):238–247.
4. Couto B, Tartaglia MC, Kovacs GG, Lang AE. Ethnic background and distribution of clinical phenotypes in patients with probable progressive supranuclear palsy. Differences in progressive supranuclear palsy in patients of Asian ancestry? Parkinsonism Relat Disord 2025;130:107179.
5. Parmera JB, Coutinho AM, Aranha MR, et al. FDG-PET patterns predict amyloid deposition and clinical profile in corticobasal syndrome. Mov Disord 2021;36(3):651–661.
6. Angel MJ, Mizraji GF, Gomez-Arevalo G, et al. Prospective longitudinal cohort of Argentinean patients with progressive supranuclear palsy and corticobasal syndrome: a platform for epidemiological and translational research. Clin Park Relat Disord 2025;12:100339.
7. Couto B, Fox S, Tartaglia MC, et al. The Rossy progressive supranuclear palsy Centre: creation and initial experience. Can J Neurol Sci 2023;50(6):845–852. https://doi.org/10.1017/cjn.2022.332