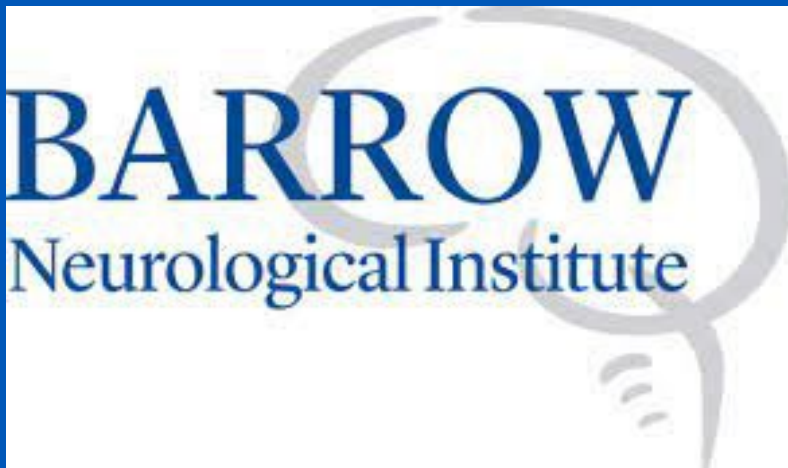




Mild Behavioral Impairment is Associated with Postmortem Alzheimer’s Disease Neuropathology



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BACKGROUND

The time-honored challenge in the field of the neuropsychiatry of Alzheimer's Disease (AD) is delineating Neuropsychiatric Symptoms (NPS) that occur in the context of AD versus primary psychiatric disorders. This spurred the development of the construct of Mild Behavioral Impairment (MBI), defined as the new onset of persistent NPS at ≥50 years of age. Little is known about whether MBI is associated with AD neuropathology in a population-based setting. NPS are frequently observed in AD and related dementias. We have reported associations between NPS, including MBI and cognitive and biomarker measures. We sought to extend our study to include postmortem neuropathology measures as the outcomes.

OBJECTIVES

To examine the associations between MBI and postmortem AD neuropathology (Braak stage, CERAD score, Thal phase) as well as cerebrovascular pathology (Kalaria score) in the population-based Mayo Clinic Study of Aging.

METHODS

The study included 421 deceased participants from the Mayo Clinic Study of Aging, with NPS data whose last MCSA visit occurred within 5 years of death (mean interval 1.8 years) and no psychiatric history before MCSA recruitment. Participants were ≥50 years of age at MCSA enrollment and were cognitively unimpaired (CU) or had mild cognitive impairment (MCI) at entry. All autopsies were performed between 2005 and 2025.

METHODS

NPS were assessed primarily with the informant-based Neuropsychiatric Inventory Questionnaire (NPI-Q), supplemented by self-reported measures, the Beck Depression Inventory-II (BDI-II) and the Beck Anxiety Inventory (BAI). AD neuropathology included: Braak stage (0–VI) for neurofibrillary tangles, Thal phase (0–5) for amyloid-β plaque distribution, and CERAD score (none/sparse /moderate/frequent) for neuritic plaque density. Cerebrovascular pathology was quantified using the modified Kalaria score (0–20).

Linear regression models were run for the outcomes of Braak and Kalaria. Proportional odds logistic regression models were run for the outcomes of Thal and CERAD. Separate models were run using MBI TTV (defined as having MBI based on NPI-Q for at least two-thirds of study visits [TTV] for those with 2+ visits), and MBI (defined as having at least one NPI-Q variable indicated) at the last visit before death as predictors. All models were adjusted for age at last visit, sex, and education.

CONCLUSIONS

- In this population-based neuropathology study, persistent MBI was associated with greater amyloid plaque burden (CERAD, Thal phase).
- MBI at the last visit prior to autopsy showed a stronger and more consistent association across all AD pathology (amyloid plaque burden and NFT). Additional analysis is warranted as 16% of participants had progressed to dementia by last visit.
- MBI was not associated with cerebrovascular pathology.
- The differential pattern - persistent MBI associating more strongly with amyloid measures while last-visit MBI robustly associated with all three measures, including tau - might suggest long-standing NPS may reflect earlier amyloid-driven processes, while recent symptoms might track advancing tau pathology.

Funding: This work was supported by NIH (R01 AG057708 and U01 AG006786) and the Barrow Neurological Foundation. The Mayo Clinic Study of Aging was supported by the following sources: NIH U01 AG006786, R01 AG034676, R37 AG011378, R01 AG041851, R01 AG056366, R01 AG068206, P30 AG062677, GHR Foundation, Elsie and Marvin Dekelbaum Family Foundation, Liston Award, Schuler Foundation, Alexander Foundation, Mayo Foundation for Medical Education and Research.

RESULTS

- Mean (SD) age at last visit was 86.6 (6.2) years; 41% were women.
- Persistent MBI was associated with higher CERAD scores and higher Thal phase.
- MBI at the last visit showed stronger associations across all three AD pathology measures, including a robust link with Braak stage.
- No statistically significant associations were observed between MBI and Kalaria scores.

TABLE 1: Overview at last visit

Variable	Overall (N=421)
Age at last visit	86.6 (6.2)
Female	173 (41.1%)
Education, years	14.7 (3.2)
Number of visits*	1.6 (1.8)
MBI at last visit	197 (46.8%)
Braak stage	3.4 (1.4)
CERAD frequent^	104 (25.4%)
Thal phase 5	66 (18.5%)
Kalaria score	4.4 (2.5)

Mean (SD) or n(%); missing data for Braak stage (6), Thal phase (64), CERAD (12) and Kalaria (99) scores. *number of visits with NPS indicated; CERAD frequent neuritic plaques.

Table 2. MBI and NPS associations with neuropathology

Exposure	Outcome	Estimate*/OR** (95% CI)	P-value
Persistent MBI	Braak stage	$\beta = 0.22 (-0.13, 0.56)$	0.22
Persistent MBI	CERAD	OR 1.86 (1.19, 2.93)	0.007
Persistent MBI	Thal phase	OR 1.81 (1.13, 2.90)	0.014
Persistent MBI	Kalaria	$\beta = 0.15 (-0.52, 0.82)$	0.66
Cumulative NPS (IQR)	Braak stage	$\beta = 0.108 (0.028, 0.188)$	0.008
Cumulative NPS (IQR)	CERAD	OR 1.75 (1.26, 2.43)	0.001
Cumulative NPS (IQR)	Thal phase	OR 1.60 (1.15, 2.21)	0.005
Cumulative NPS (IQR)	Kalaria	$\beta = 0.055 (-0.119, 0.229)$	0.53
Last-visit MBI	Braak stage	$\beta = 0.41 (0.22, 0.60)$	0.001
Last-visit MBI	CERAD	OR 1.68 (1.22, 2.31)	0.001
Last-visit MBI	Thal phase	OR 1.79 (1.28, 2.51)	0.001
Last-visit MBI	Kalaria	$\beta = -0.16 (-0.64, 0.32)$	0.51

*Linear regression models adjusted for age, sex, education and numbers of visits.

**Proportional Odds Logistic Models adjusted for age, sex, education and numbers of visits.

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