

Cerebral small vessel disease markers differentially associate with neuropsychiatric vulnerability in dementia with Lewy bodies

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Background

Dementia with Lewy bodies (DLB) is characterized by prominent cholinergic dysfunction and often coexists with cerebrovascular co-pathology.¹ Cerebrovascular lesions (CVL), notably lobar cerebral microbleeds (CMB) and white matter hyperintensities (WMH), are markers of cerebral vulnerability associated with cognitive impairment in older adults²⁻⁴ and may contribute to cholinergic degeneration in Lewy body disease.¹ Their role in early neuropsychiatric symptoms (NPS) of DLB remains insufficiently characterized.

Objective

To explore the relationship between common MRI markers of CVL, including CMB and WMH, and NPS in clinically diagnosed DLB.

Methods

Clinically diagnosed DLB cases (n=70) followed at the Cognitive Neurology Division of the Geneva University Hospitals (HUG) were analyzed. CMB were assessed visually on MRI obtained during the clinical diagnostic workup, and WMH were assessed using standardized visual rating scales: the Fazekas scale for global burden and the Cholinergic Pathways Hyperintensities Scale (CHIPS) for WMH within cholinergic pathways.^{1,5}

NPS, including depression, anxiety, apathy, hallucinations, delusions, and delirium, were assessed retrospectively from medical records. NPS other than delirium were evaluated at the first cognitive assessment. Delirium was considered present if documented within the 12 months preceding DLB diagnosis. Descriptive analyses were performed. Cross-sectional associations between CVL markers and NPS were examined using regression models adjusted for age, sex, and educational level.

Characteristic	Total sample (n=70)
Age at initial visit, mean (SD), y	78.9 (7.7)
Female sex, n (%)	18 (25.7%)
MOCA score at baseline, mean (SD)	15.7 (7.4)
Education level, mean (SD)	2.1 (0.7)
Amyloid co-pathology, n/N (%)	11/16 (68.8%)

Table 1. Baseline demographic and clinical characteristics

Continuous variables are presented as mean (SD) and categorical variables as n (%). Sample sizes varied across variables owing to missing data. Amyloid co-pathology data were available in a subset of 16 patients.

Abbreviations: MOCA, Montreal Cognitive Assessment

Results I

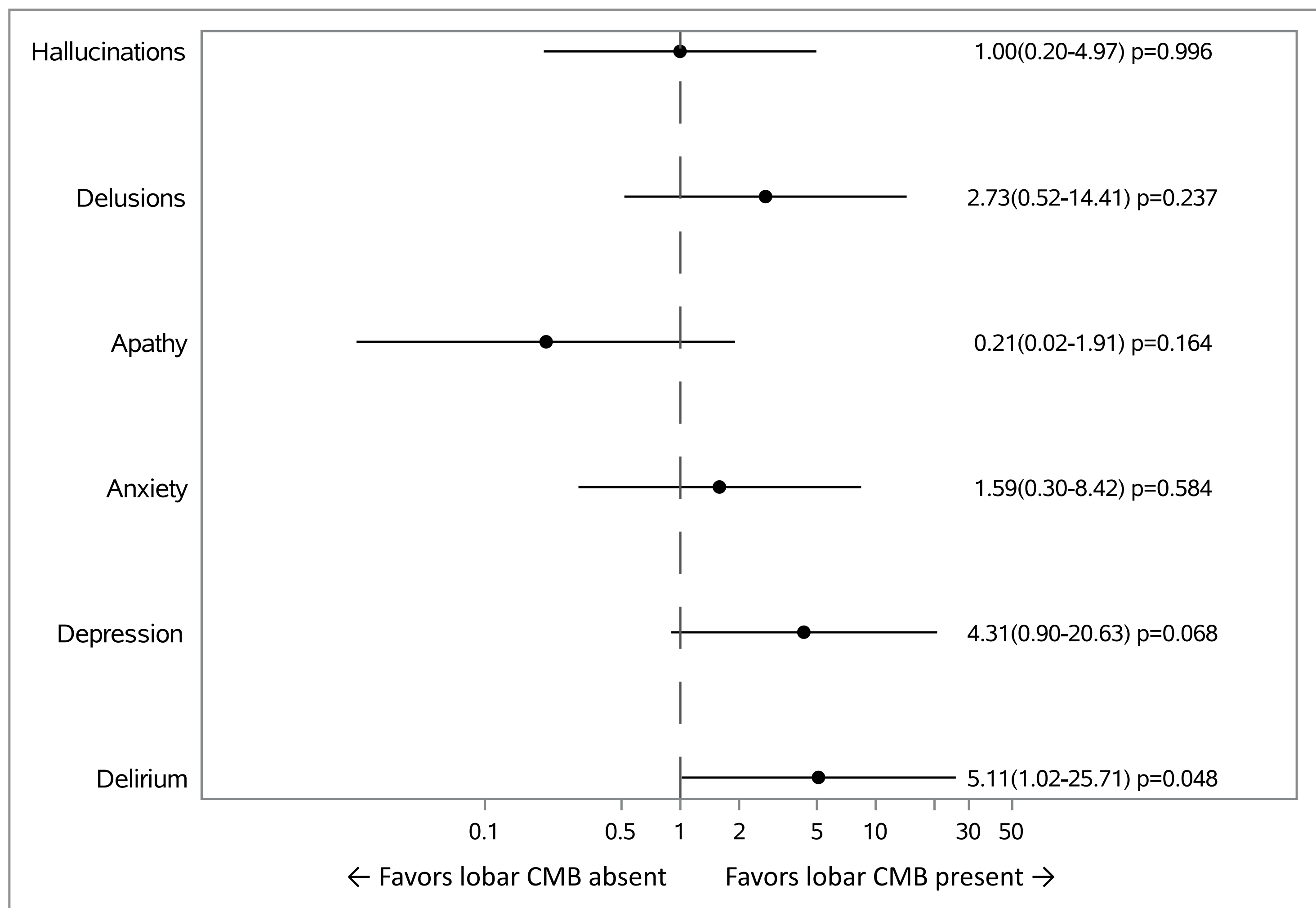


Figure 1. Association of lobar cerebral microbleeds with neuropsychiatric symptoms
Adjusted odds ratios (OR) with 95% confidence intervals (CI) derived from logistic regression models adjusted for age, sex, and educational level. The dashed vertical line indicates OR = 1 (no association). In sensitivity analyses, the MB-delirium association was attenuated in Firth logistic regression, used to reduce sparse-data bias (OR, 4.27; 95% CI, 1.10-23.89; P=.06).

Outcome	CHIPS adjusted OR (95% CI)	p-value	Fazekas adjusted OR (95% CI)	p-value
Depression	0.95 (0.87–1.03)	0.220	0.74 (0.31–1.76)	0.499
Anxiety	0.91 (0.83–0.99)	0.034	0.50 (0.18–1.35)	0.169
Apathy	0.97 (0.90–1.04)	0.413	0.77 (0.29–2.02)	0.590
Delusions	1.15 (1.04–1.29)	0.010	1.03 (0.33–3.26)	0.961
Hallucinations	0.99 (0.93–1.06)	0.763	1.27 (0.50–3.19)	0.614
Delirium	1.03 (0.96–1.10)	0.467	1.55 (0.57–4.19)	0.390

Table 2. Association of white matter hyperintensity burden (Fazekas and CHIPS scores) with neuropsychiatric symptoms

Odds ratios (OR) with 95% confidence intervals (CI) were derived from regression models adjusted for age, sex, and educational level. Sample sizes were 45/47 (CHIPS/Fazekas) for apathy, delusions, hallucinations, and delirium; 41/43 for depression; and 40/42 for anxiety, owing to outcome-specific complete-case analyses. Reported P values are uncorrected for multiple comparisons.

Results II

CMB were present in 17 of 54 cases (31.5%), and 45 of 69 patients (65.2%) had at least 1 documented delirium episode in the year preceding diagnosis. In adjusted analyses, cMB were associated with prediagnostic delirium (OR, 5.11; 95% CI, 1.02-25.71; P=.048), whereas the association with depression did not reach statistical significance (OR, 4.31; 95% CI, 0.90-20.63; P = .07). No significant associations were observed with anxiety, apathy, hallucinations, or delusions. WMH burden assessed with the Fazekas scale was not associated with any neuropsychiatric outcome, whereas CHIPS showed associations in opposite directions with anxiety (OR, 0.91; 95% CI, 0.83-0.99; P = .03) and delusions (OR, 1.15; 95% CI, 1.04-1.29; P = .01).

Limitations

- Modest sample size with outcome-specific complete-case analyses.
- Firth sensitivity analysis attenuated the primary association.
- Preliminary exploratory analyses using a retrospective cross-sectional design with multiple comparisons, requiring further validation in larger longitudinal cohorts

Conclusion

In this exploratory cross-sectional study of 70 clinically diagnosed DLB cases:

- **Lobar CMB were associated with prediagnostic delirium, suggesting a potential vascular contribution to early neuropsychiatric expression.**
- **The association between lobar CMB and neuropsychiatric symptoms appeared specific to delirium, with no significant associations observed for depression, anxiety, apathy, hallucinations, or delusions at first cognitive assessment.**
- **Global WMH burden (Fazekas) was not associated with any neuropsychiatric outcomes, whereas cholinergic pathway WMH (CHIPS) showed selective associations with anxiety and delusions.**
- **Together, these findings support a differential contribution of CVL to the prodromal neuropsychiatric phenotype of DLB, underscoring the need to better define the role of cerebrovascular pathology in Lewy body disease.**

References

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