

# CSF $\beta$ -amyloid and white matter damage: unravelling the neuropathology of Alzheimer's disease

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## White matter lesion load may be associated with lower CSF $\beta$ -amyloid levels in Alzheimer's disease (AD) subjects.

The great advance of neuroimaging techniques witnessed in the last 10 years has enabled an intensive debate on the role of white matter (WM) lesions in the pathophysiology of AD. Once regarded by the early literature as a common result of cerebrovascular pathology, WM alterations, particularly those found in predementia stages, have been consistently linked to neurodegeneration processes by recent multimodal studies. One particular relevant issue is whether WM primary degeneration evolves independently from grey matter (GM) atrophy or occurs as a secondary product of cortical atrophy, as posited by the Wallerian degeneration hypothesis.<sup>1,2</sup> The work from Pietroboni *et al*<sup>3</sup> thus sheds light on this theme by investigating some putative mechanisms linking amyloid deposition and WM load in patients with low and high  $AB_{1-42}$  levels.

The authors have found, as one of the core findings, a closer association of higher WM changes and lower  $\beta_{1,42}$  cerebrospinal fluid (CSF) levels in AD subjects. In fact, it has been proposed that factors such as microglial activation may promote neurotoxic and oligodendrotoxic AD pathology, spreading through WM damage.<sup>4</sup> But some studies found contrasting evidence, for instance, CSF total tau, but not  $\beta_{1,42}$  CSF levels, as associated with WM microstructural changes (radial and mean diffusivity proxies).<sup>4</sup> But which lessons could be learnt from this paper?

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1. A broad evaluation with macrostructural and microstructural measurements was performed by including  $\beta_{1,42}$  CSF levels, diffusion-weighted images, WM lesion load (WMLL) and GM volumetric analysis.
2. The work explored candidate thresholds of normality of  $AB_{1-42}$  levels in which is possible to find a stronger correlation with WMLL.
3. WM primary degeneration was found as an early feature of AD, apparently independent from age status and the evolution of GM atrophy. Furthermore,  $\beta_{1,42}$  CSF levels were the best predictors for the WMLL accumulation. Converging evidence supporting these findings has been indicated by other studies.<sup>5</sup>
4. As GM volume was significantly decreased in all patients compared with controls and GM reduction was explained by CSF levels on a 36% variance, it is possible to hypothesise that WM and GM loss share CSF tau levels as a predictor of atrophy.

Hence, the findings reported by Pietroboni *et al* provide additional evidence on the importance of multimodal neuroimaging as a robust approach in the investigation of AD-related WM pathology; it also offers important insights on the overlapping mechanisms linking amyloid deposition and WM primary neuropathology.

The specific molecular mechanisms driving neuronal disconnection in the landscape of AD pathology, and whether WM-related changes are more associated with tau or  $\beta$ -amyloid pathology, remain to be further elucidated by upcoming studies.

**Competing interests** None declared.

**Provenance and peer review** Commissioned; internally peer reviewed.



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**To cite** Sousa Alves G. *J Neurol Neurosurg Psychiatry* Published Online First: [please include Day Month Year]. doi:10.1136/jnnp-2017-317053

Received 19 October 2017

Accepted 13 November 2017



► <http://dx.doi.org/10.1136/jnnp-2017-316603>

*J Neurol Neurosurg Psychiatry* 2017;0:1.  
doi:10.1136/jnnp-2017-317053

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