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Can tauopathy shake the amyloid cascade hypothesis?

Venugopalan Y. Vishnu

In an article in the February 2013 issue of this journal (Alzheimer disease: Aβ-independent processes—rethinking preclinical AD. *Nat. Rev. Neurol.* 9, 123–124; 2013),[1] Gaël Chételat discusses the roles of tau and amyloid in Alzheimer disease (AD) pathology. The article was based around the findings of a 2013 publication by Knopman *et al.*[2] that reported neuronal injury in the absence of substantial amyloid burden. After two decades of chasing evidence for the amyloid hypothesis of AD, and after the recent disappointments in immunotherapy trials, it is imperative that alternative hypotheses are considered and actively pursued. New models are emerging that present opportunities for therapeutic research. The amyloid hypothesis was again questioned in the article by Chételat.[1] 'Amyloid-β (Aβ)-independent process' is an exciting concept, but is there enough evidence to warrant a rethinking of the amyloid cascade hypothesis?

The concept that amyloid pathology occurs upstream of neurodegeneration by tau has been the cornerstone of the amyloid hypothesis. In autopsy studies, however, tau pathology has been observed before marked Aβ deposition. In a study of brains from young individuals (between 4 and 29 years of age), Braak and Del Tredici observed pre-tangles that were positive for AT8 (an anti-tau monoclonal antibody) as early as the first decade of life.[3] Notably, many genetic tauopathies are not associated with significant dementia.[4] Presence of tau from the first decade of life to old age in the absence of dementia could indicate, therefore, that tau is a marker of ageing.

Jack *et al.*[5] recently proposed an integrative model in which subcortical tau is the initial pathological event, with amyloid pathology developing independently of, and possibly accentuating, tauopathy. Although evidence exists to suggest that tauopathy begins before initiation of the amyloid cascade, whether tauopathy alone can initiate AD pathogenesis remains unclear. Studies in early-onset (familial) and late-onset (sporadic) AD have shown that Aβ is the disease initiator.[6,7] The study by Knopman *et al.*[2] reveals that Aβ-independent pathology probably does exist, but to say that this finding challenges the amyloid hypothesis is premature as evidence in favour of the amyloid hypothesis is strong, in particular with regard to genetically determined AD.

In her model of the pathological mechanisms underlying AD, Chételat has given equal importance to Aβ and tau pathology,[1] which, in my opinion, is stretching the point too far. By depicting Aβ and tau symmetrically in the figure, the impression is that two factors are acting equally, but evidence to support this theory is lacking. Although tau pathology may occur earlier than amyloid pathology or may have a pathogenic role in a small percentage of patients, much research remains to be done before attribution of a definite pathogenic role to tauopathy ahead of amyloid accumulation. Based on currently available evidence, Aβ—either as initiator or as an accelerator of disease—is still the main factor in the pathogenesis of AD.

Department of Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India.
vishnuvy16@yahoo.com

Competing interests
The author declares no competing interests.

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