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EDITORIAL

Tau pathology in children and young adults: can you still be unconditionally baptist?

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The lesions of Alzheimer Disease (AD) pathology, senile plaques and neurofibrillary tangles, are made of an accumulation of Aβ peptide in the extracellular space and of tau protein in the neurons. The discovery that a mutation of the amyloid precursor protein (APP) gene was able to induce AD, naturally led to conclude that Aβ was the initiator and tau, the follower. The "cascade hypothesis" according to which the trigger is Aβ accumulation [8] was further supported by the finding that mutations of *MAPT*, the tau gene, cause a pure tauopathy without Aβ accumulation [9, 13].

The cascade hypothesis remains our current framework of interpretation. It predicts that Aβ accumulation precedes tau pathology. Recently, for instance, Jack et al. [10] proposed a hypothetical sequence of biomarkers, illustrated by a diagram (Fig. 1b) in which Aβ precedes "tau-mediated neuronal injury and dysfunction". It should be stressed, however, that neuropathological data do not fit this hypothetical representation. Braak et al. [2] have shown, as early as 1997, that tau pathology in the entorhinal-hippocampal region precedes Aβ accumulation by decades. The comparison of the curves drawn from Braak et al. data (Fig. 1a) [5] with the hypothetical diagram of Jack et al. (Fig. 1b) is striking. Although the curves have similar shapes, tau pathology precedes amyloid deposition by 27 years in the data of Braak and Braak [2, 5].

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It now appears that this delay may even be much longer. In this issue of *Acta Neuropathologica*, Braak and Del Tredici [3] show that tau-positive material, labeled by the AT8 monoclonal antibody, is visible in a high proportion of children and young adults in the absence of Aβ accumulation (except in one case suffering from trisomy 21). The topography of these changes suggests a sequence that, in its most advanced stage, merge with the lowest Braak's [1] classical neurofibrillary stages: AT8-positive neurons are located either in the locus coeruleus alone, in the locus coeruleus and in other subcortical nuclei (all with diffuse cortical projections), or in the above-mentioned nuclei as well as in the transentorhinal cortex (Braak's neurofibrillary stage I). While this represents exciting and unexpected news, a few major issues remain to be resolved. What is the significance of the AT8-positive material? Is it irreversible? Which proportion of AT8-positive changes is in a fibrillary form due to tau aggregation, a process that seems to be crucial to pathogenesis [11]?

Tau pathology seen in children and young adults, if confirmed, could modify our view on AD as deeply as the unexpected finding that young soldiers, killed in action in Korea, had signs of coronary atherosclerosis [6]: AD might not be a disease of the aged, but, as atheroma, a life-long disorder.

The observation that tau pathology is detected decades before any Aβ deposition does not immediately discard the cascade hypothesis: high levels of Aβ could be present very early in a soluble form (as shown in Down syndrome [15]), or in some cell compartments [14], and be responsible for a slow alteration of tau metabolism even in the absence of Aβ deposits. The senile plaque would then be an epiphenomenon, indicative of a high concentration of Aβ but not responsible for the cascade of subsequent events. Alternatively, tau and Aβ accumulations could be, at least

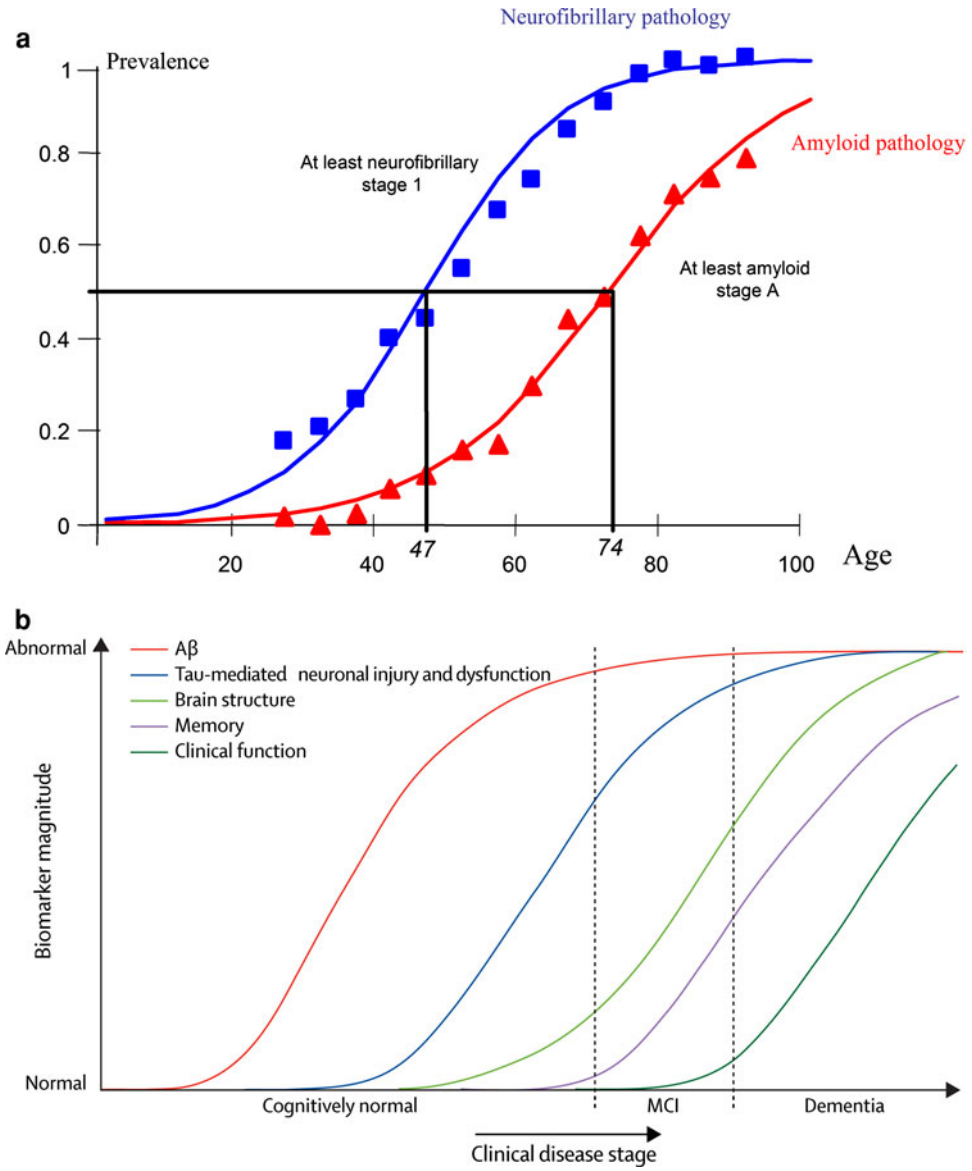

Fig. 1 **a** Prevalence of the lesions in the series of 2,661 cases studied by Braak and Braak [2] and their logistic estimates [5] (figure slightly modified with permission). *Blue squares* observed frequency of cases with at least Braak's neurofibrillary stage 1. *Red triangles* observed frequency of cases with at least Braak's amyloid stage A. The *lines* were interpolated by logistic regression. Neurofibrillary tangles were present in half of the population at the age of 47; amyloid deposits were observed in half the population at the age of 74 as indicated. **b** Dynamic biomarkers of the Alzheimer's pathological cascade Aβ are identified by CSF Aβ42 or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. *Aβ* β-amyloid, *MCI* mild cognitive impairment (from [10] with permission). Discrepancies between **a** and **b** may be due to various causes: **a** describes prevalence while **b** illustrates severity; limited tauopathy in trans/entorhinal areas may be too subtle to be detected by peripheral markers; neuropathology detects *visible* alterations, and changes in concentrations could occur earlier; tau peripheral markers could be poorly sensitive. On the other hand, neuropathological observation indicates that tau intraneuronal accumulation is at least an early (if not the first) event in the cascade that leads to AD

partially, independent but synergistic processes. There are evidences that tau pathology once initiated may go on by itself. In an inducible model, tau pathology progressed after the expression of the mutated tau transgene had been shut down (whereas memory function recovered) [12]. This observation may be combined with recent evidences that fibrillary tau, even exogenous, induces tau aggregation in connected neurons in a manner reminiscent of prion spreading through neural circuits [4]. Once started at one point of the neural network, tau pathology could thus spread independently of Aβ accumulation. One could also imagine that the high level of Aβ could promote tau aggregation [7] that would have taken place by itself but at a much slower pace.

The cascade hypothesis, in its primitive form, has probably led to an underestimation of the role of tau in AD pathogenesis. Or more precisely, tau pathology is probably misplaced in the cascade. It may explain why the current, Aβ oriented, therapeutic attempts have not been as successful as expected. AD remains a two-faced disorder and now as ever, the connection between tau and Aβ pathology remains one of the most important unsolved questions of AD research. As they frequently did in the past, Braak and Del Tredici have again demonstrated that mere, but careful, observation of facts must be the inseparable companion of theory.

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