Alzheimer disease: Aβ-independent processes-rethinking preclinical AD.

Gaël Chételat

Aβ-independent processes-rethinking preclinical AD

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The 20-year dominating amyloid cascade hypothesis posits that Aβ accumulation is the primary and causal event in Alzheimer disease neurodegeneration. Recent findings, however, show that neuronal-injury biomarkers are independent of Aβ. This will probably lead calling for reconsideration of the pathological cascade and assessment of alternative therapeutic strategies.

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An unexpected conclusion on preclinical Alzheimer disease (AD) pathology, which was made following a series of important studies by a group at the Mayo Clinic, Rochester, MN, USA, constitutes a turning point in AD research. In the latest study, published in *Annals of Neurology*,[1] cognitively normal elderly individuals with amyloid-β (Aβ) deposition (with or without neuronal injury) were compared with individuals with neuronal injury but no Aβ deposition. As Aβ is thought to initiate the pathological cascade of AD, the former group were thought to be in the preclinical stage of AD, whereas the latter group was designated as suspected non-AD pathology (SNAP). However, the data showed that the two groups were indistinguishable on a variety of imaging markers, clinical features and risk factors, and led the authors to conclude that the initial appearance of brain injury biomarkers in cognitively normal elderly may not depend on β-amyloidosis.

The path to this conclusion began a few years ago in the context of lively enthusiasm for Aβ imaging as a tool for early diagnosis of AD, but also as a method to ultimately prove or disprove the Aβ hypothesis. In 2010, Clifford Jack and colleagues from the Mayo Clinic proposed a model, largely based on the amyloid cascade hypothesis, which integrated the most thoroughly validated biomarkers of AD pathology.[2] This model reflected the typical progression of the disease in which Aβ biomarkers become abnormal first, followed by neurodegenerative biomarkers themselves preceding cognitive symptoms.

One year later, the National Institute on Aging-Alzheimer's Association published recommendations on the definition of preclinical AD for research purposes.[3] On the basis of the conceptual model of Jack *et al.*, the preclinical phase of AD was proposed to encompass three sequential stages: stage 1 (amyloidosis), in which only Aβ biomarkers are abnormal (or positive); stage 2, in which both Aβ biomarkers and biomarkers for neuronal injury are positive; and stage 3, with evidence of subtle cognitive impairment.

In June 2012, these criteria were operationalized and applied to a population-based sample of 450 cognitively normal elderly.[4] In this sample, 43% had no abnormal biomarker (stage 0). 31% of the individuals fell within stages 1 to 3; these patients were considered to have entered the AD pathway, and thus would progress to AD. 23% of the sample, however, had neuronal injury without evidence of Aβ deposition. As this finding did not follow the sequence of the model, the category was not thought to represent a stage of preclinical AD, but rather a distinct, biologically based category of SNAP. Scientific support for this interpretation was thus fervently warranted.

Such support was expected from a parallel publication by the same group, in which the short-term clinical outcomes for each stage of pathology were evaluated.[5] The researchers found that conversion to MCI or dementia increased across most stages, but the results were inconclusive with regard to the SNAP group, probably owing to the short follow-up and modest number of individuals who converted to MCI or dementia (none converted to AD). Of those with SNAP, 10% converted within 1 year—a conversion rate not markedly different to that seen in patients with preclinical AD stage 0 (5%), stage 1 (12%), or stages 1-3 combined (18%). Nevertheless, the SNAP group remained classified as preclinical non-AD individuals.

Results from the most recent study, however, have led to reconsideration of this interpretation.[1] The investigators compared the SNAP group to those with preclinical AD stages 1-3 on a variety of measures. As the most frequent non-AD pathophysiological processes are cerebrovascular disease and synucleinopathy, individuals with SNAP were expected to differ from preclinical AD on these parameters. However, the two groups were indistinguishable on any measures of cerebrovascular risk factors or α-synucleinopathy, and thus the authors concluded that the initial appearance of brain injury biomarkers in cognitively normal persons may not depend on Aβ amyloidosis.

This conclusion has major implications for AD. It contradicts not only earlier statements that SNAP represents non-AD pathology and that preclinical AD initiates with Aβ, but also the

sequential biomarker model of AD and—perhaps of greatest consequence—the amyloid cascade hypothesis.

Arguments against the new findings include the fact that Aβ imaging mainly measures fibrillar Aβ and not the more-toxic soluble form; however, both forms are thought to be in equilibrium in AD. An additional concern is that the results rely on the sensitivity of imaging techniques, and other related methodological issues must be considered, such as the definition of criteria for thresholds and regions of interest. Despite such issues, we can no longer ignore that neuronal injury can, at least partly, occur independently of Aβ-related processes. Further evidence of support has begun to accumulate, the most recent of which include studies showing neuronal injury independent of Aβ deposition in Apoliprotein-E4 carriers[6] and studies in carriers of mutations that lead to the early-onset familial form of AD, in which neuronal injury was evident before or at the same time as Aβ deposition.[7,8]

We are entering an era in which it is likely that the unitary view of AD as a disease with a single sequential pathological pathway, in which Aβ is considered as the only initial and causal event, will be progressively replaced with a more complex picture in which AD is considered as a multiparameter pathology subtended by several partly independent pathological processes. Regional discrepancies in the degree of atrophy, hypometabolism[9] and amyloid deposition[10] lead to similar conclusions: Neuronal injury may have different causes in AD, and various sequences of pathological events could occur (Figure 1). It is possible, for example, that Aβ and tau (and possibly other) pathologies occur partly independently – influenced by both independent and common risk factors. Once both pathologies are present they would interact to promote the AD neuropathological cascade. Indeed, evidence exists to suggest that tau promotes Aβ toxicity and that Aβ activates tau toxicity.

According to this new view, one might consider all CSF and neuroimaging biomarkers (plus the presence of subtle cognitive deficits and even of subjective cognitive impairment) equal, with the additive presence of each feature causing an incremental increase in the risk of these features to represent AD pathophysiological process and in the risk for the individual to progress to AD. Even atrophy and hypometabolism could be considered as partly independent processes.[9] Cognitive impairment is thought to occur following brain changes, but in some cases may be experienced or evident before detectable alterations in the brain. The timing of cognitive impairment will depend on interindividual variability, cognitive reserve and

compensation processes, and thus it may be preferable to consider cognitive impairment separately (instead of sequentially) as for other biomarkers of AD.

The proposal of SNAP has been a short-lived but relevant and useful concept as it led to the hypothesis that AD-related neuronal injury may be independent from Aβ. Future research will reveal whether this view is true and if it will dominate, but what is certain is that this claim will provoke lively debate in the AD research community.

[1] INSERM, U1077, Caen, France

Correspondence to: G. Chételat
chetelat@cyceron.fr

Competing interests

The author declares no competing interests.

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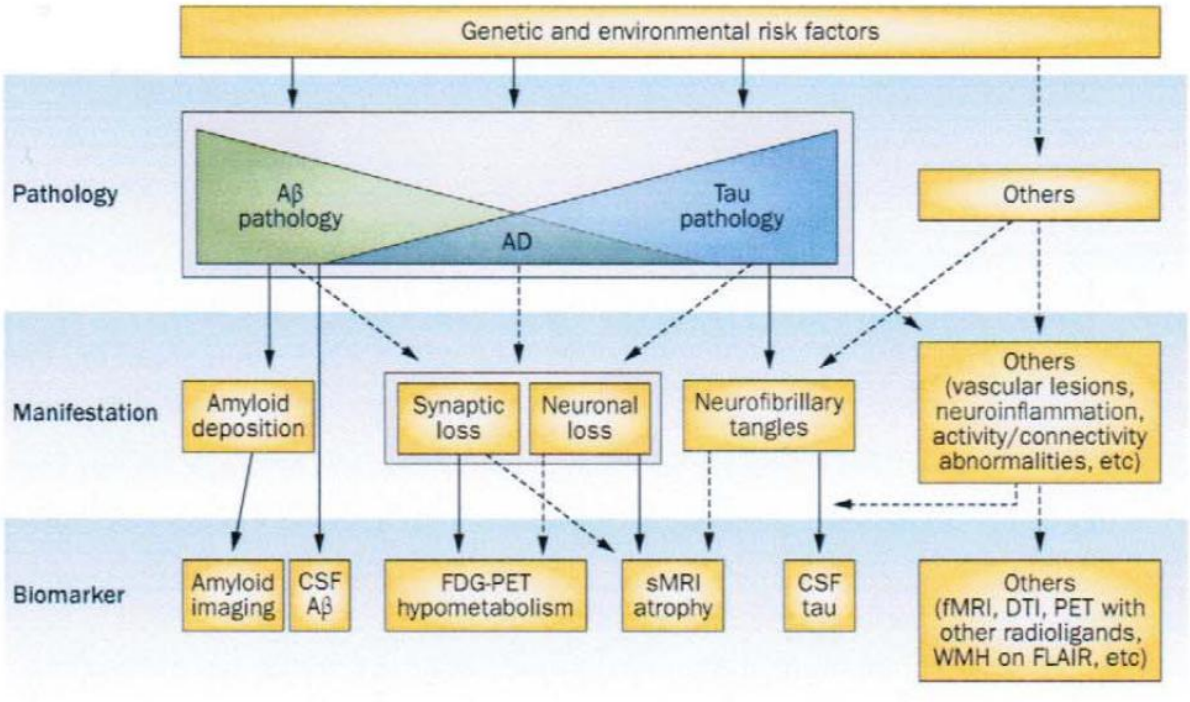

Figure 1: Possible mechanisms for AD considering Aβ deposition and neuronal injury as (partly) independent events. Aβ and tau-related pathologies may occur in parallel, their onset and rate being under the influence of a series of genetic and environmental risk factors. These pathologies result in brain alterations that are then represented in neuroimaging measures classically used as biomarkers for AD. Abbreviations: Aβ, amyloid β; CSF, cerebrospinal fluid; FDG, ^{18}F-fluorodeoxyglucose; fMRI, functional MRI; sMRI, structural MRI; WMH, white matter hyperintensities.