Journal Club

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β-Amyloid Accumulation Slows Earlier than Expected in Preclinical Alzheimer's Disease Patients

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Review of Leal et al.

Alzheimer's disease (AD) is the most common form of dementia, and epidemiological studies suggest that the rates of incidence will increase in the next decades (Prince et al., 2013). Clinically, AD is manifested by progressive memory loss, but the main pathophysiological hallmarks include accumulation of β-amyloid (Aβ) peptides, formation of neurofibrillary tangles containing hyperphosphorylated forms of the microtubule-associated protein tau, and synaptic failure.

Levels of Aβ, found both as soluble oligomers or insoluble extracellular plaques, are almost invariably increased in AD patients' brains and according to the amyloid cascade hypothesis of AD pathogenesis, this accumulation is the initial pathological event leading to synaptic and cognitive dysfunction (Hardy and Higgins, 1992; Gong et al., 2003). However, this hypothesis remains somewhat controversial (Selkoe, 2013; Drachman, 2014). Indeed, the discovery that some individuals without any overt signs of dementia carry significant cerebral amyloid deposits suggests that Aβ plaques are not sufficient to cause AD (Herrup, 2015). A variation of the amyloid hypothesis accounts for this finding by proposing that soluble Aβ oligomers, instead of Aβ plaques, are responsible for cognitive impairment in AD (Haass and Selkoe, 2007). But some authors have suggested that, although brain Aβ levels are elevated in AD, this is merely a consequence of upstream problems, rather than being the cause of the disease (Drachman, 2014). Possible upstream problems include neurovascular dysfunction, unbalanced glucose homeostasis, failure in neuronal cell cycle control, and inflammation (Herrup, 2015). In support of this hypothesis, signs of neuroinflammation can be observed before Aβ deposition in AD mice models (Kummer et al., 2014). The failure of large clinical trials to demonstrate the effectiveness of potential disease-modifying treatments suggests that our understanding of the molecular basis of AD is incomplete (Mehta et al., 2017).

It is argued that the failure in these clinical trials stems partly from the challenge in discriminating the earliest stages of AD, leading to the inclusion of patients whose therapeutic window has already closed. Currently, cognitively normal patients who reach a threshold of brain Aβ plaque load based on positron emission tomography (PET) imaging using a radioactive analog of thioflavin T, ^{11}C-Pittsburgh Compound B (PIB), are classified as having preclinical AD (Klunk et al., 2004; Sperling et al., 2011). This classification might set thresholds too high to detect earlier stages of disease (Villeneuve et al., 2015). Identifying biomarkers that reliably discriminate the initial stages of AD and determining when these markers should be measured might therefore improve AD therapeutics.

In a recent article published in *The Journal of Neuroscience*, Leal et al. (2018) longitudinally evaluated AD-associated biomarkers in 71 cognitively normal elders. Specifically, PIB and [^{18}F] AV-1451 PET brain imaging were used detect amyloid and tau plaques, respectively. The difference between the first PIB measurements (basal levels) and after an average of 4.5 years was used to define the rate of Aβ plaque accumulation in the brain. Surprisingly, the authors found an inverted-U relationship between the Aβ plaque accumulation rate and Aβ basal levels. In other words, in the subset of this preclinical AD population with a higher baseline Aβ burden, the Aβ plaque deposition rate was slowing down, suggesting saturation of Aβ plaque formation in the brain. Furthermore, a higher rate of Aβ plaque accumulation was the best predictor of future abnormal tau levels in neocortical brain regions, followed by initial levels of Aβ (Leal et al., 2018). The authors

Received June 23, 2018; revised Aug. 29, 2018; accepted Aug. 30, 2018.

This work is supported by CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico, Grant 148929/2016-8) and FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo, Grant 17/01339-2). We thank Laís Ferreira (Federal University of Rio de Janeiro) and Dr. Sudhir Tattikota (Harvard Medical School, Boston, MA) for helpful insights. We also thank Dr. Teresa Esch for relevant editorial comments.

The authors declare no competing financial interests.

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DOI:10.1523/JNEUROSCI.1592-18.2018

 0270-6474/18/389123-03$15.00/0

concluded that the brains of preclinical AD elders have pathological modifications that predict future hallmarks of the disease.

Next, Leal et al. (2018) evaluated the correlation between brain Aβ profile in preclinical AD patients and memory decline as assessed by verbal learning and visual reproduction tests. Correlations were analyzed in three subsets of participants, classified according to basal PIB values. Individuals with basal PIB levels <1.07 were classified as PIB negative, and participants with basal PIB levels <1.30 (including PIB-negative participants) were classified as low PIB, while the participants with basal PIB levels >1.30 were classified as high PIB. In PIB-negative people, neither basal levels of Aβ plaques nor the rate of amyloid deposition predicted memory loss. In low-PIB participants, an increase in the amyloid deposition rate was the best predictor of cognitive decline. Finally, when including low-PIB and high-PIB preclinical AD participants, basal levels of Aβ best predicted memory loss (Leal et al., 2018). Importantly, a parallel study reinforced the correlation between the rate of Aβ accumulation and memory decline in elders, strengthening the concept that the rate of amyloid accumulation is a good predictor of future AD pathology (Landau et al., 2018). The authors suggested that the correlation between memory decline and Aβ plaque accumulation in the low-PIB group indicates that disease is still spreading in individuals with the lowest Aβ burden. When the disease advances, reaching high basal levels of Aβ, the initial amyloid burden better predicts future memory decline (Leal et al., 2018).

Leal et al. (2018) analyzed their findings in terms of the amyloid cascade hypothesis of AD. Thus, they propose that the correlation between faster Aβ accumulation and abnormal tau levels seen on PET imaging stems from Aβ triggering cortical tau deposition. The authors also proposed that their data are consistent with the hypothesis that Aβ plaque increases precede tau deposition, and both precede memory impairment. Based on that interpretation, they suggest that antiamyloid therapies should be started even earlier than expected, in preclinical AD patients with fast accumulation of Aβ plaques, otherwise the disease would be too advanced to be effective. If that is true, the inclusion of these patients in future clinical trials could elucidate the real efficacy of antiamyloid therapies and the recommended intervention window.

As noted above, however, some researchers dismiss the amyloid hypothesis, suggesting that the linear model of Aβ leading to cognitive impairment is insufficient at best (Drachman, 2014). Moreover, the amyloid cascade hypotheses do not answer some questions arising from the results of the study by Leal et al. (2018). For example, why did some participants accumulate amyloid faster than others? Leal et al. (2018) observed that faster Aβ plaque accumulation predicts higher tau levels, but the authors measured tau only at the end of the study. An intriguing possibility is that Aβ "fast accumulators" actually had higher levels of tau in the beginning of the study, which caused their amyloid levels to increase. Recently, it was shown that N-terminal fragments of tau can induce Aβ secretion *in vitro* (Bright et al., 2015), and autopsy evidence suggests that tau phosphorylation precedes Aβ deposition in some individuals (Jack et al., 2013). Also tau, but not Aβ, induced morphological abnormalities in the microvasculature of the brain and induced plasminogen activator inhibitor-1 activation in microglia in AD experimental models (Bennett et al., 2018), and both of these events are associated with neuronal death (Drachman, 2014). Therefore, tauopathy might be the primary driver of future cognitive decline.

Another interpretation of the data from the study by Leal et al. (2018) is that the amyloid deposition rate in patients with preclinical AD reflects an already toxic brain environment, which independently modulates Aβ accumulation and neuronal death (Drachman, 2014). When the brain detects homeostatic imbalance, microglia are activated, culminating into neuroinflammation. Accordingly, proinflammatory signaling is activated in the brains of AD patients (Heneka et al., 2015). Microglia activation promotes Aβ clearance by phagocytosis in mice in a process mediated by TREM2, a cell surface protein highly expressed in microglia that directly binds to Aβ (Zhao et al., 2018), which could explain the slowing down of Aβ plaque deposition in patients with higher amyloid burden. Cross talk between angiogenesis and neuroinflammation occurs during the progression of AD, as shown by TNF-α-dependent microglial activation inducing blood–brain barrier disruption (Nishioku et al., 2010). Therefore, neuroinflammation could simultaneously affect levels of Aβ plaques and brain functionality. In future studies, the use of PET probes for markers of immune competent cells, such as $(^{11})$C-PBR28 for measuring TSPO (translocator protein 18 kda) (Kreisl et al., 2013), and the measurement of cerebral blood flow (Roher et al., 2012) would shed light on the causality of amyloid and other AD hallmarks during disease progression.

A comprehensive understanding of the primary neurological changes in AD is essential for the development of more effective early intervention. Leal et al. (2018) provided data showing that the rate of amyloid plaque accumulation is the best predictor of future abnormal tau levels and memory decline in patients with preclinical AD with the lowest amyloid burden, demonstrating that Aβ measurement is suitable for predicting AD pathology. However, because the causality of Aβ depositions remains controversial, if amyloid deposition is not the fundamental cause of AD, clinical trials targeting amyloids are predicted to fail, even if applied in patients in the early stages of the disease. Thus, future investigations should use longitudinal approaches to measure simultaneously other AD hallmarks, such as neuroinflammation, tau alterations, and brain vascularization. This will improve our understanding of causality in AD, paving the way for the development of alternative therapies for treating AD.

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