Consequences of redefining Alzheimer’s disease in terms of amyloid burden without regard to cognitive decline

Alzheimer’s disease (AD) redefined: For the past century, AD has been defined as a disease of progressive cognitive decline paired with a burden of amyloid-β (Aβ) plaques and pathologic tau tangles in the hippocampus and forebrain. However, a recent Framework paper jointly sponsored by the National Institute on Aging and the Alzheimer’s Association (Jack et al., 2018) proposes new classification guidelines for AD, which, if adopted, will have profound consequences for the future management of AD. The new guidelines redefine AD in terms of the brain’s burdens of Aβ and to a lesser extent tau, regardless of cognitive status (Figure 1). This biological approach is consistent with other diseases (e.g., type 2 diabetes) that are defined and managed in terms of biomarkers, rather than on the basis of overt symptoms. This redefinition of AD is expected to greatly facilitate progress in clinical trials and therapeutics.

Recasting Aβ burden as the primary defining feature of AD will allow the success of clinical interventions to be evaluated on the basis of whether they are able to diminish the burden of Aβ, without the need to demonstrate that cognitive decline was present or has been arrested. These relaxed guidelines will make it easier to claim success at treating AD. While the new guidelines have been proposed for sound reasons, the present authors are concerned that they will lead to adverse outcomes for patients, and could prevent progress towards a genuine cure for AD.

Advantages of a biomarker definition of AD: The influential ‘Amyloid cascade hypothesis’ postulates that toxic complexes of Aβ damage the brain, eventually causing progressive cognitive decline. Over the past two decades, more than 200 clinical trials have been conducted with the specific aim of reducing the Aβ burden in AD patients order to arrest the progression of dementia. Some trials have achieved impressive reductions in Aβ burden, yet none have slowed the cognitive decline (Brothers et al., 2018). With the worldwide number of cases of AD growing strongly, the massive size of the untapped market for AD therapeutics has led pharmaceutical companies to invest heavily in the area. However, the cost of funding a series of unsuccessful clinical trials has begun to take its toll: in January 2018, Pfizer Inc. announced that they will lead to adverse outcomes for patients, and could prevent progress towards a genuine cure for AD.

Ethical and clinical considerations for anti-Aβ therapeutics: Pharmaceutical companies that undertake clinical trials to attack Aβ in midlife will need to address the psychological risks associated with patients being labelled with AD, decades before cognitive decline becomes apparent. A parallel can be found in Huntington’s disease, where genetic screening is used to reveal carriers during the pre-symptomatic phase: such knowledge can enable an individual to plan for their future, yet it is also associated with higher rates of aggression, hopelessness, anxiety, depression and suicidal ideation (Anderson et al., 2016). The imperfect correlation between Aβ load and subsequent conversion to AD raises additional concerns. A considerable body of evidence has demonstrated that many elderly individuals with high levels of Aβ never develop progressive cognitive decline or dementia (Perez-Nievas et al., 2013). Initiating anti-Aβ therapies in the absence of any cognitive deficits will inevitably result in some individuals receiving unnecessary treatment, while increasing their risk of depression and anxiety.

Another consideration relates to the adverse outcomes that commonly arise from depleting the brain of Aβ. Clinical trial reports of anti-Aβ therapeutics indicate that the incidence of cerebral edema and micro-bleeds increases nearly five-fold following the initiation of therapy, and can lead to headache, confusion, nausea and gait disturbances. Indeed, these unpleasant symptoms are so prevalent, occurring in up to half of the patients in some immunotherapy trials, that they are referred to euphemistically as ‘ARIA’ (amyloid-related imaging abnormalities). Other adverse outcomes include increased rates of meningocencephalitis and re-emergent infections (Brothers et al., 2018). This situation begs the question of whether it is ethical to knowingly expose cognitively normal people to the risk of these adverse outcomes, particularly when it will not be known for decades whether anti-Aβ therapy in midlife reduces the risk of developing dementia in old age.

In addition to its involvement in AD, Aβ is produced by the brain throughout life where it appears to serve several important physiological roles, including the clearance of amyloid from the brain, patching breaches of the blood-brain barrier and assisting in the consolidation of memories [reviewed by Brothers et al. (2018)]. Thus, it may prove necessary to screen participants in...
anti-Aβ clinical trials for the remainder of their lives, to ensure that the neutralisation of Aβ's physiological functions does not increase the rates of cerebral infection, micro-bleeds or memory loss. Evidence suggests that Aβ may assist the nervous system to recover from other forms of injury; BACE1 knockout mice and Aβ-precursor protein (APP) knockout mice both have a 40% survival rate within 4 hours of cerebral ischemia, compared to 100% survival rates in wild-type mice (Koike et al., 2012). Likewise, in mice subjected to a spinal cord injury, prevention of Aβ production by BACE1 knockout or γ-secretase inhibition results in impaired motor recovery and more extensive white matter damage (Pajoohesh-Ganji et al., 2014). Conversely, AD-transgenic rats, which overexpress Aβ, have reduced infarct volumes compared to wild-type rats following occlusion of the middle cerebral artery; the transgenic rats perform better on tests of spatial memory and fear conditioning than the wild-type rats, despite worse outcomes on motor tasks (Clark et al., 2007). Further, in four different mouse models of multiple sclerosis, intracerebral injection of hexameric Aβ1-42 or Aβ1-40 led to improvements in motor function, remyelination of lesions and reduced inflammation (Grant et al., 2012). Collectively, these studies suggest that focusing AD therapeutic strategies on the depletion of Aβ may impair the capacity of patients to recover from neurological injuries, of which the elderly are at an increased risk.

Conclusion: While focusing AD drug development on the reduction of Aβ burden offers certain advantages for clinical trials, it may result in unintended consequences, including a diminished capacity to recover from stroke and brain injury, psychological repercussions of believing they have AD, as well as the risk of adverse side-effects like ARIA and meningoencephalitis. If active immunotherapies are used, the autoimmune response against Aβ will be lifelong, potentially extending these risks over decades. What if the amyloid cascade hypothesis is wrong? Some researchers have argued for a causative role of tau in AD pathogenesis, whereas others have proposed that Aβ plaques are part of an innate response to brain injury (Robinson and Bishop, 2002). Animal and human studies have shown that Aβ deposition can be induced by a wide range of events that are injurious to the brain including TBI, stroke and hypoxia (Brothers et al., 2018). Although the Framework paper acknowledges that there is uncertainty regarding whether Aβ plaques are the cause or a consequence of the disease process (Jack et al., 2018), the biological definition implies that the presence of a higher-than-normal burden of Aβ is AD. In effect, the amyloid cascade has been elevated from a hypothesis to a definition of AD in research or in clinical trials. For this reason, and those outlined in the preceding paragraphs, we caution against adopting the proposed biological definition of AD in research or in clinical trials.

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