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Once upon a time, the Amyloid Cascade Hypothesis

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ABSTRACT

Recent trials with monoclonal antibodies targeting amyloid-β (Aβ) in Alzheimer's disease (AD) have sparked a renewed interest in disease-modifying therapies. Despite their promise, these trials leave the issue open and posit some doubts about the validity of the Amyloid Cascade Hypothesis (ACH). While some scores of neurocognitive tests improved upon treatment, real-world clinical benefits were minimal. This Viewpoint discusses additional, often overlooked findings from these trials. We also emphasize the multifactorial nature of AD and the need for a broader research perspective beyond the simplistic disease model provided by the ACH.

"Science must begin with myths, and with the criticism of myths." – Karl Popper.

The implementation of aducanumab, lecanemab, donanemab, solanezumab, and gantenerumab – monoclonal antibodies designed to wipe out the pathological accumulation of amyloid-β (Aβ) – thrilled the field of Alzheimer's disease (AD) as a much-needed and long sought game-changer in the treatment of the disease. However, the data suggests a different story.

Let us start with the rationale for this line of intervention. The amyloid cascade hypothesis (ACH), now in its 30 s, posits the accumulation of Aβ as the primary trigger for a series of molecular events that favor the production of hyperphosphorylated tau aggregates, the activation of neuronal death mechanisms and, eventually, dementia (Hardy and Higgins, 1992). In the following decades, the ACH has been updated to incorporate and integrate accumulating preclinical, clinical, imaging, and genetic data and the effect of stochastic factors (Frisoni et al., 2022). Despite its evolution, the ACH backbone remained: Aβ is the killer, tau the smoking gun, and neurons the victims. This quantifiable triad also served for an unbiased staging of the AD continuum and is at the basis of the "ATN research framework". The system is designed to provide a biological definition of AD (i.e., 'A' – amyloid, 'T' – tau, and 'N' – neurodegeneration) (Jack et al., 2018) and spurred the idea that changes in AD-related biomarkers can be considered efficacy outcomes or a proxy of efficacy in clinical trials for AD. This interpretation supported the recent and highly controversial accelerated approval by the Federal Drug Administration (FDA) of aducanumab and lecanemab. The decision was primarily based on the reported reduction of Aβ plaques (Federal Drug Administration, 2023). The results of the aducanumab and lecanemab studies reignited a critical appraisal of the ACH. The last few months have generated a flurry of papers that, with different degrees, provided arguments in support or against the ACH (Daly et al., 2022; Haass and Selkoe, 2022; Daly, 2023; Hardy and Mummery, 2023; Høilund-Carlsen et al., 2023; Kepp et al., 2023b, 2023a; Liu et al., 2023; Perneczky et al., 2023; Rollo et al., 2023; Young-Pearse et al., 2023). The controversy became hot, reminiscent of the old Baptists vs. Tauists debate (Mudher and Lovestone, 2002). Of note, doubts and criticisms regarding the ACH have persisted since its inception. Critiques emerged early on and targeted fundamental aspects of Aβ biology that are still debated today, including the poor correlation between amyloid deposits and cognition (Terry, 1996) as well as the overlooked and largely unexplored role of the peptide as a protective, compensatory response to age-related insults elicited via its antioxidant and neurotrophic-like activities (Whitson et al., 1989; Perry et al., 2000). Nevertheless, the tantalizing – and easily verifiable – causal linearity of the ACH, quickly paved the way for the development and testing of Aβ-lowering drugs.

The latest results from the trials of donanemab – whose approval is expected by the end of 2023 - and solanezumab, two other monoclonal antibodies designed to clear brain amyloid plaques, might help to draw a clearer picture and, despite the mediatic *spins and hype*, argue against the validity of the ACH (Sims et al., 2023; Sperling et al., 2023). Some overlooked observations are worth discussing.

Lack of disease-modifying behavior – The lecanemab and donanemab

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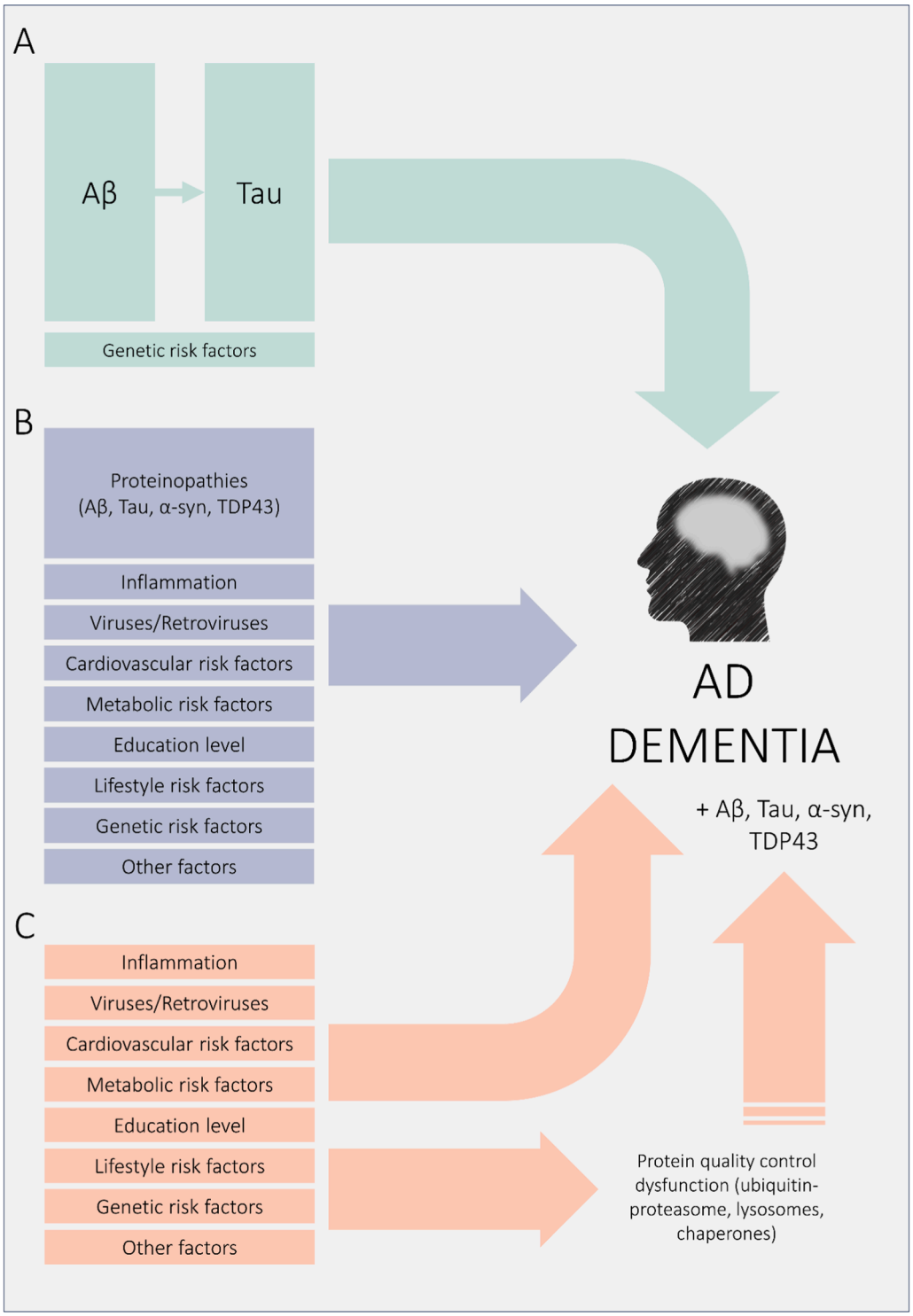

Fig. 1. A still uncertain route to dementia. The diagram illustrates three putative disease models of AD. A) The top flowchart illustrates a simplified view of the ACH; Aβ dysmetabolism leads to amyloid and Tau protein deposition eventually triggering, neuronal death, brain atrophy, and dementia. Genetic factors contribute, with different degrees, to shape the risk of developing Aβ- and Tau-pathology. B) The middle diagram depicts a non-linear, multifactorial disease model in which the combination of molecular (including protein misfolding), genetics, and lifestyle factors – individually or in association – contribute the development and progression of AD. C) The bottom flowchart depicts an alternative view in which the combination of many molecular, genetic, and epigenetic factors shape the disease process. In parallel these factors also impair cellular systems in charge of protein disposal (lysosomes, ubiquitin-proteasome system, chaperones) thereby producing the build-up of misfolded proteins (Aβ, Tau, α-syn, TDP-43) that is not per se the cause of the disease but rather the molecular signature of failing clearance mechanisms. Thus, in this case the removal of amyloid only helps cleansing the brain of deposits of discarded proteins while minimally affecting the course of the disease.

studies showed a statistically significant reduction in the clinical progression of AD as measured by a handful of scores of neurocognitive tests (Sims et al., 2023; van Dyck et al., 2023). Aducanumab-driven score changes were statistically significant in the EMERGE but not in the sister ENGAGE trial (Budd Haeberlein et al., 2022). Notably, the changes in test scores translated poorly into clinical effects as perceived by patients and caregivers. More importantly, an analysis of the trajectories of the disease progression indicates that Aβ immunotherapy groups diverge from placebo in the first 36 weeks of treatment but then proceed in parallel. This contrasts with what one would expect with disease-modifying drugs, as disease trajectory should increasingly diverge.

An unexplainable shrinkage - The Aβ immunotherapy trials revealed a puzzling phenomenon: accelerated brain volume loss and ventricles enlargement in treated people (Alves et al., 2023). A clear explanation of this drug-induced effect is missing. However, the changes (quantified to be in the order of several milliliters) are unlikely due to the removal of Aβ plaques (estimated to account for <10 μl of brain volume) (Ayton, 2021). It is also worth noting that the result contradicts what is posited by the ACH and the ATN constructs. How do we reconcile a drug that wipes completely out the "putative" cause of the disease, i.e., senile plaques, but exacerbates one of its key, most relevant features, i.e., brain/neural loss? Of note, during the latest Alzheimer's Association International Conference (AAIC), an update of the ATN criteria has been proposed to devalue the "N" – neurodegeneration – to a non-specific, second-tier biomarker (Bowman Rogers, 2023). An alternative, more conservative explanation suggests that an immunotherapy-mediated reduction of brain inflammation drives such volume changes. The hypothesis contrasts with the analysis from Alves and colleagues, showing that amyloid and volume loss are spatially, temporally, and quantitatively disconnected (Alves et al., 2023). Accordingly, the phenomenon is better explained as a consequence of ARIAs. Furthermore, limited and conflicting reports exist regarding the impact of Aβ opsonization on the inflammatory profile of microglia (Strohmeyer et al., 2005; Franco-Bocanegra et al., 2019; Da Mesquita et al., 2021). Nevertheless, without patient-level data, any interpretation remains speculative.

Missing the most vulnerable – ApoE4 carriers and women are particularly susceptible to AD. Thus, these two groups should be expected to benefit the most from disease-modifying pharmacological interventions. Again, this is not the case. Aβ immunotherapies are less effective in ApoE4 carriers (van Dyck et al., 2023) than non-carriers. They also produce more frequent and severe side effects (Sims et al., 2023) in these carriers. Moreover, the drugs fail to provide a more significant benefit in female patients (Budd Haeberlein et al., 2022; van Dyck et al., 2023). Sex subgroup analysis shows minimal benefits following antibody administration, primarily occurring in males, not females (Budd Haeberlein et al., 2022; van Dyck et al., 2023). Only donanemab exerted similarly modest effects on both sexes (Sims et al., 2023).

A deceptive statistic – Several methodological factors are called into question when dealing with trial failures. In this context, statistical flaws are often overlooked. A recent retrospective analysis examined the issue by leveraging on a Bayesian approach. Simply put, unlike classical (or frequentist) methods that rely on a fixed, predetermined set of rules to analyze data, Bayesian methods continuously update and refine the outcome as more and more information is gathered, reflecting a flexible and adaptive approach to understanding treatment efficacy. The analysis revealed a grim picture, demonstrating that passive immunotherapy interventions in AD did not have a significant effect (Costa et al., 2023a, 2023b).

The A4 trial. A tombstone for the ACH? – The case was frequently made that late intervention was the primary cause for the failures of Aβ-targeting strategies. The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) trial was designed to circumvent such limitations. The trial targeted cognitively intact elderly individuals with elevated amyloid levels as assessed by PET imaging, a feature "believed" to be the biomarker of a preclinical, asymptomatic stage of AD (Sperling et al., 2023). Solanezumab, a monoclonal antibody targeting monomeric Aβ forms, was employed in these subjects to reduce Aβ accumulation. The 4.5-year-long trial failed. Solanezumab reduced amyloid build-up by several centiloids, indicative of target engagement, but was ineffective in slowing down cognitive decline or accumulation of tau in critical brain areas (Sperling et al., 2023). Of note, although lacking statistical significance, the trajectories of the cognitive performances of the solanezumab-treated group were consistently worse than those observed in the placebo group (Sperling et al., 2023). This empirical observation aligns with the hypothesis that decreased levels of soluble monomeric Aβ could participate in AD-related cognitive decline (Espay et al., 2021; Sturchio et al., 2022; Imbimbo et al., 2023).

What are we missing? – The seductive epistemological simplification offered by the ACH has permeated and influenced almost every aspect of AD research to the point that AD cannot be investigated without dealing with Aβ-related mechanisms. Several permutations of the original hypothesis have been proposed (Daly, 2023). However, real-life data indicates a more complex scenario in which an almost uncountable network of factors interact and shape the disease risk at an almost patient-specific level (Fig. 1). Several findings substantiate this idea. 1) Population studies identify a robust fraction of elderly subjects – roughly 60% of the individuals aged > 85 years – with a pathological Aβ burden that is cognitively intact (Jack et al., 2019; Knopman et al., 2021), arguing against a simplistic series of cause-effect events as posited by the ACH. 2) Post-mortem analysis of the neuropathological features of cognitive-impaired elderly subjects revealed that the co-existence of multiple neuropathologies is extremely common (Boyle et al., 2018), questioning the idea of a single pathogenetic determinant. Furthermore, statistical modeling suggests that this mixed-neuropathology accounts only for a small fraction of the cognitive decline, with at least fifty percent of the variation in cognitive decline remaining unexplained (Boyle et al., 2021). These findings suggest the presence of yet unidentified factors that can shape the brain's resilience to neuropathological challenges. It is also worth mentioning that the weight of these neuropathological changes decreases when approaching the terminal stages of the decline (Boyle et al., 2021). As Richard Feynman said: "There is plenty of room at the bottom". 3) The last 30 years have witnessed a downward trend in the incidence of dementia in industrialized countries (Tom et al., 2020). A favorable but unexpected decrease is likely explained by profound societal changes that shape the risk of developing dementia and disclose easily targetable modifiable factors (Livingston et al., 2020; Frisoni et al., 2023). Recent estimates identify 12 risk factors that account for around 40% of worldwide dementias (Livingston et al., 2020). Many more can have a small but substantial impact at a person-specific level (Rolandi et al., 2020).

A blank silver bullet? Given the past setbacks and the modest results shown by Aβ targeting trials, it is evident that a one-size-fits-all approach and the conceptual monopoly of the ACH are no longer tenable. Sadly, disappointment was predicted over two decades ago, but the warning has been disregarded (Smith et al., 2002). Persisting in pursuing a miraculous cure will continue to drain ideas, resources, and enthusiasm.

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Declaration of Competing Interest

none.

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