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Editorial

Road to Alzheimer's in the light of evolution β-amyloid: villain or hero down?

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The age of 65 years is generally used to classify Alzheimer's disease (AD) as early-onset or advanced-onset, corresponding to 10% of rare forms with onset at younger ages, with clear familial aggregation, autosomal dominant inheritance, and identified mutations coding for enzymes which catalyze the production of amyloid peptide (A) from amyloid precursor protein (APP).

This essay refers to the sporadic form, without going into detail (this is not a review) to the intensive and extensive molecular studies related to AD. Likewise, and without the slightest intention of ignoring them, we also do not refer to other marginal hypotheses that arise about the cause of AD.

In theory, the central histopathological finding for both forms, although present with greater intensity in the early-onset form, is the accumulation of β-amyloid peptide (AβP) in the brain, which has given rise to the hypothesis known as the "amyloid cascade" (ACH). The process begins with the aggregation of Aβ peptide in plaques, leading to a neurodegenerative cascade that in turn triggers the aggregation of a tangle of neurofibrils composed primarily of hyperphosphorylated tau protein, resulting in disseminated neuronal death, all of which points to its contribution to brain pathology and resulting dementia.

Thus, over several decades, experimental focus has centered on this ACH, with pharmacological strategies promoting dissolution, arrest, and ideally prevention of the process. However, virtually exclusive adherence to this hypothesis has been questioned for the following reasons: *postmortem* studies show that one-fourth to one-third of older adults without AD show Aβ plaques with varying density; in this regard, proponents of ACH point out that the density of tau protein tangles, whose formation is triggered by Aβ plaques, correlates closely with disease severity.

On the other hand, about one-third of clinically diagnosed cases of AD do not show an accumulation of Aβ on PET scanning. What is relevant to note, however, is the continued failure over the last 15 years, of studies focusing on Aβ over more than 400 controlled clinical trials, and although some drugs have reduced Aβ levels, no clinical improvement has been observed in any case.

The proteolytic process involving APP, which gives rise to Aβ, has been viewed as normal and not as a pathological pathway exclusive to AD. Aβ, far from being unique to AD, is widely distributed in the living world and its structure has been conserved with very little change over more than 400 million years of evolutionary time; it is present in most vertebrates, further supporting the idea that, far from being a catabolic waste by-product, it must rather have an important adaptive physiological function. Indeed, there is significant compelling evidence that Aβ has important antibiotic properties, such that it has come to be classified as a member of the antimicrobial peptide (AMP) family. It is well known that innate

immunity and AMPs play a major role as defenses in "immunologically privileged" organs such as the brain where, given the risk of immunopathological responses in tissue with almost no regenerative capacity, acquired immunity is severely restricted.

These observations motivate us to consider a paradigm shift in the investigation of the cause and possibilities of treatment and prevention of AD. There is strong evidence that antimicrobial activity is exerted precisely through the generation and accumulation of Aβ; microbial pathogens become entangled in the tangle of neurofibrils and are permanently trapped within the Ab deposits. All this has led to considering an infectious etiology for an AD so that a *"Pathogen hypothesis"* has been put forward, which could be interpreted as an alternative hypothesis to that of the amyloid cascade. However, in a way, there has been an inconvenient shift from one simplistic hypothesis to another, where different groups of researchers each have their favorite microorganism, trying to identify the specific "culprit" causing AD, with the hasty yearning for antimicrobials or vaccines. However, "don't throw the baby out with the bath water"; the amyloid cascade may be a key intermediary on the Pathway to Alzheimer's disease. The two hypotheses must then be combined. It is important to note that the pathogen hypothesis does not necessarily refer to a specific microorganism; indeed, there is evidence that the accumulation of Ab may be caused by brain lesions accompanied by "sterile" inflammation or by oxidative stress.

Age is a clear risk factor for AD, which from an evolutionary point of view has a logical explanation. Our genome has not had time to adapt to the longer life expectancy achieved by medical and public health measures. The survival achieved is not accompanied by better health conditions; on the contrary, nutritional transitions and lifestyles different from those to which our genome was shaped in the Paleolithic period some 15,000 years ago and much further back, have left the human species vulnerable to disease. The average life expectancy in those hunter-gatherer times was about 35 years. Thus, the accumulation of Aβ may have evolved as an adaptation, the product of a process that comes to confer adaptive value (*Darwinian fitness*), i.e. the ability of individuals to survive and reproduce. Natural selection does not design organisms to be healthy; only to the extent that health contributes to reproductive success; in other words, natural selection is "not interested" in the conservation of health after the reproductive peak (around 25 years of age). On the other hand, adaptations, in general, have a cost, and, as a complement to defense mechanisms, maintenance processes have evolved -evolutionarily- that try to prevent or repair the damage inherent to defenses which, like other maintenance and repair mechanisms, tend to weaken progressively with age. In other words, adaptations are generally accompanied by *trade-offs,* becoming rather maladaptive under certain conditions; in this case, the fundamental condition would be age, in which the adaptive value conferred by the antimicrobial protection of Aβ is achieved at younger ages at the price of AD at older ages.

The hypotheses and facts that emerge from the intensive research to try to explain the pathogenesis of AD can be coherently integrated within reasonably established principles of evolutionary medicine. The evolutionary approach allows better targeting of research on molecular (proximal) aspects, broadens the view in the interpretation of the results, and, more importantly, minimizes risks to human health. It should be kept in mind that the human body is not a machine that can simply be repaired but is the product of 3.5 billion years of evolution. In fact, within the new paradigm of Developmental Origins of Health and Disease (DOHaD), based on evolutionary and developmental principles, epigenetic changes related to aging, induced by either environmentally or stochastically have been found. This would offer potential opportunities for intervention, since these epigenetic changes induce, especially in the early stages of development, plasticity that to some extent would allow reversing deleterious effects, acting even from the intrauterine nutritional environment, which could condition a greater susceptibility to diseases associated with aging, including Alzheimer's disease.

The need for markers to alert to the ongoing formation of Aβ has been satisfied in principle by measuring concentrations of phosphorylated tau in cerebrospinal fluid, as well as non-invasive methods such as PET scanning. Interestingly, the finding of a protein called IFITM3, which -significantly in suggestive relation to the pathogen hypothesis- is activated by viruses trying to enter the brain, a protein which in turn activates Aβ-forming enzymes.

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Despite the lack of convincing evidence that the reduction of Aβ results in clinical improvement, and despite even accepting that Aβ is not the causative agent, but a *surrogate* marker (*surrogate; proxy),* the FDA, based on studies showing a decrease in the accumulation of Aβ measured by PET scan, approved in June 2021 -for the first time in the history of ACH- the clinical use of Aducanumab, a monoclonal antibody targeting the accumulation of Aβ, a decision based on the fact that, according to studies conducted by the pharmaceutical company Biogen, it is "reasonably likely to predict a clinical benefit". Thus, surprisingly, the FDA sets aside its usual regulatory route of requiring evidence of clinical efficacy, although it cautiously warns Biogen that it must conduct a Phase 4 study to "verify clinical benefit", and if the results are inconclusive, the approval could be canceled.

This strange procedure by the FDA has, of course, aroused heated controversy. Since Aducanumab will not be applied to "very advanced" cases of AD, where the alleged benefit concerning the cost ($56,000 per year!) is not to be expected, and given the observation that previous studies on Aβ reduction have been performed late when the damage caused by amyloid accumulation would be irreversible, the requirement is that Aducanumad in the clinic is applied to "moderate" (criteria?) cases showing the existence of Aβ accumulation by PET scanning or by markers in the cerebrospinal fluid. The patient is supposedly told that there is ambiguity about the benefit. The exclusion of advanced cases of AD in clinical trials means that recruitment of participants is done at relatively early stages of the disease in the face of supposedly greater effectiveness of Aβ reduction. If the accumulation, as proposed by the pathogen hypothesis, were acting as a defense, a potentially dangerous infection could be triggered. The pathogen hypothesis has been ignored in this whole process leading to the approval of Aducanumab for clinical use. The likely side effects of reducing the accumulation of Aβ should have included the incidence of viral and other infections. Now, infectious diseases of the central nervous system must be included as a probable adverse effect in the agreed Phase 4 study protocol which, although it came about by an odd route, offers a unique, invaluable opportunity to obtain evidence for or against the pathogen hypothesis.

Recommended readings

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