Alzheimer's Disease Really Start

Subjects: Pathology

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While Alzheimer's disease (AD) classical diagnostic criteria rely on clinical data from a stablished symptomatic disease, newer criteria aim to identify the disease in its earlier stages. For that, they incorporated the use of AD's specific biomarkers to reach a diagnosis, including the identification of Aβ and tau depositions, glucose hypometabolism, and cerebral atrophy. These biomarkers created a new concept of the disease, in which AD's main pathological processes have already taken place decades before we can clinically diagnose the first symptoms. Therefore, AD is now considered a dynamic disease with a gradual progression, and dementia is its final stage. With that in mind, new models were proposed, considering the orderly increment of biomarkers and the disease as a continuum, or the variable time needed for the disease's progression. In 2011, the National Institute on Aging and the Alzheimer's Association (NIA-AA) created separate diagnostic recommendations for each stage of the disease continuum—preclinical, mild cognitive impairment, and dementia. However, new scientific advances have led them to create a unifying research framework in 2018 that, although not intended for clinical use as of yet, is a step toward shifting the focus from the clinical symptoms to the biological alterations and toward changing the future diagnostic and treatment possibilities.

Keywords: dementia ; AD spectrum ; biomarkers ; CSF ; AD dynamic ; imaging biomarkers

1. Introduction

With the advent of biomarkers came a conceptual change of the disease. We moved from a "static and defensive" view of the pathogenesis of AD to a "dynamic and compensatory" point of view. In the first viewpoint, the brain lesions that lead to neuronal and synaptic loss and finally to cognitive deterioration depend on the degree of external aggression and on the structural reserve that each person has. The current view considers an inter-individual variability in the response to these initial aggressions, as well as differences in the severity of the pathological process and in the efficiency and evolution over time of the cerebral compensatory mechanisms [1][2][3]. Therefore, the idea that AD's main pathological processes have already taken place before we can clinically diagnose MCI has been established, and this is reinforced by the fact that these lesions begin even decades before the appearance of the earliest symptoms, when the subject is still cognitively normal [4]. Therefore, this change in perspective increasingly supports the need for early therapeutic action in order to compensate for those biological processes that are already compromised before the onset of the cognitive failure [5].

2. When Does Alzheimer's Disease Really Start?

AD is now considered a neurodegenerative disease with a very long evolution that starts silently decades before the onset of symptoms and advances gradually and slowly until it compromises the person′s cognition. Therefore, we moved from a static vision of AD in which a person is affected or not by the disease, to a dynamic concept of AD, in which dementia is considered the final stage of a set of pathological changes that occur in a chronic and gradual manner.

In this progression, which may take years, biomarkers can anticipate the clinical manifestations of dementia and, as the new diagnostic criteria introduced biomarkers in a supporting role in AD's diagnosis, many laboratories worldwide have already started using them. With this in mind, and based on determinations made in different populations, Jack and collaborators proposed a model for the evolution of AD over time, known as "the dynamic biomarker cascade model" [6]. In this model, biomarkers do not increase all at once but do so in an orderly manner, a concept that is reinforced in the work by Dubois and collaborators [7]. The model presents three phases along the continuum of the disease—first, the cognitively normal asymptomatic phase, then the MCI phase that begins to show clinical affectation, and finally the dementia phase. All over this spectrum, the biomarkers described previously would present abnormal levels as the disease evolves and, eventually, correlate with the clinical symptoms presented by the patients.

Jack and collaborators propose as the initial event the abnormally increased levels of Aβ that would lead to the formation of cerebral amyloid plaques. This would be reflected in the decreased levels of Aβ in CSF and in the increased amyloid load in PiB-PET, and these alterations would appear while the individuals are still cognitively normal. Afterward, there would be an increase in CSF tau abnormalities followed by alterations in FDG-PET. These are biomarkers of neuronal dysfunction and neurodegeneration and correlate with the severity of clinical symptoms. Lastly, in advanced stages, structural brain changes would appear such as cortical atrophy and decreased hippocampal volume that could be detected by MRI [6].

A very recent work by Petrella and collaborators [8] developed a mathematical causal model of the dynamic biomarker cascade theory in AD, which might help to explain how these biomarkers interact and evolve over time and could potentially help patients, researchers, and medical personnel. This is a great advancement in the knowledge of the disease, but there is still a long way to go. Although, biomarkers could have a role in predicting whether a patient could convert from MCI to AD, there is not a consensus on which biomarkers could assume that role [9][10].

However, the scientific community's efforts go beyond designing computational models to determine the behaviour of different biomarkers in the evolution of the disease. Models have been designed for many different aspects of the disease, such as a model based on the amyloid cascade hypothesis, showing the effects of pathological processes such as oxidative stress, inflammation or cerebrovascular disease in the kinetic of Aβ aggregation [11]. Moreover, another model focused on synaptic loss and compensation by the reinforcement of the remaining connections [12] and, more recently, Ding et al. (2018) designed a hybrid computational approach for a more accurate disease severity classification [13].

Nevertheless, as scientists started to better understand AD's pathophysiology, the biggest challenge became designing computational models capable of predicting the efficacy of a specific treatment. To reach this objective, models have been created analysing potential treatments. Anastasio (2013) incorporated the role of estrogens in Aβ regulation into a model that can generate therapeutic predictions and the possible benefits of this therapy [14]. This model showed that estrogen could reduce Aβ and that non-steroidal anti-inflammatory drugs could provide a small additional benefit.

Furthermore, immunotherapy, probably the most promising treatment for AD at this moment, was also analysed by computational models. Diem et al. (2016), have incorporated this therapy's possible complications into their model and concluded that a failure in periarterial drainage seems to be an important mechanism [15]. Another computer simulation model pointed out that immunotherapy against Aβ might not be effective, unless it is used during early stages of AD [16] or combined with other therapies. However, a more recent model simulated the differential impact of Aβ oligomers on glutamate and nicotinic neurotransmission while under different treatments, including a passive vaccination with the monoclonal antibody solanezumab, the use of the beta-secretase inhibitor verubecestat, and of the gamma-secretase inhibitor semagacestat. They predicted a cognitive worsening in people with low Aβ baseline and an improvement in those with moderate to high Aβ levels [17].

Computational models analyzing neurotransmitters have also been created. One such model has been implemented using preclinical data available on receptor pharmacology of cholinergic and catecholamine neurotransmitters and clinical data, to predict the effects of memantine, an N-Methyl-D-aspartic acid (NMDA) inhibitor, in different phases of AD pathology [18].

Finaly, Stefanovski et al. (2019) created a computational multi-scale brain model, using the Virtual Brain Platform, and including PET and electroencephalogram, to simulate regional neural activity and hyperexcitability in AD and how it relates to Aβ. This model reveals a potential functional reversibility of large-scale alterations in AD after memantine treatment [19].

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