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JALR. New Journal, Old questions, Fresh insights.

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INTRODUCTION:

The responsibility to serve in the editorial board of a new journal in what looks an already crowded arena is a real challenge and also a leap of optimism. The figures tell us that publications in the field of Alzheimer's disease (AD) have doubled in the past 10 years (from 4,529 in 2007 up to 9,480 until November 2017, timeline of the U.S. National Library of Medicine) and new diagnostic and therapeutic tools are constantly proposed and sometimes introduced in the clinic. The neuroimaging technological advances allow to explore in detail the morphofunctional changes occurring with normal aging, as well as in mild cognitive impairment and in different types of neurodegenerative disorders. Several theories on the chain of events leading to neuronal damage and loss are tested in transgenic mouse models as well as in controlled clinical trials. These are offering more insights on the truly relevant aspects of AD by taking advantage of biochemical and genomic tools for patients selection in the new era of personalized medicine [1-3].

AD is the most frequent age-related neurodegenerative disorder, characterized by synaptic dysfunction, neuronal damage and presence of aggregates of amyloid β-protein (Aβ) and tau protein [4]. This type dementia is characterized clinically by the loss of memory, multiple cognitive impairments and changes in the personality and behavior. However clinical diagnoses can display significant phenotypic heterogeneity and also in this area recent work has been done to identify the correlates of such diversity [2, 5].

Genetic evidence, transgenic mice models and biochemical data seem to support the amyloid hypothesis of the pathogenesis of AD: Aβ molecules tend to aggregate to form oligomers, which are extremely toxic and induce neuroinflammation [6]. In a rat model the Aβ pathology has been shown to induce neuroimaging and Alzheimer-like profile of biomarker abnormalities [7].

Therapy based on the amyloid hypothesis include Aβ vaccination and passive antibody treatment, either specific monoclonal antibodies or human pooled immunoglobulins [8-13] with the common unique aim to reduce Aβ load and prevent its aggregation in soluble oligomers and insoluble fibrils. The failure of immunotherapy trials can be due to the wrong choice of the target, the wrong selection of patients or both, but the most likely cause lies in the defective and/or

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imprecise tool used to reach the ultimate goal of removing pathogenic aggregates, e.g. antibodies with the wrong spectrum of specificity. However very recent reports allow some more hope in this field [8, 14]. Many other approaches to AD therapy have been attempted in transgenic mice models, targeting different receptors/mechanisms [15-17] and the neurotransmitters'network [18] but also reconsidering the effects of diet and hormones [19, 20]. AD models are useful to assess both removal of Aβ and the reduction of neuroinflammation [21] in preclinical studies [22].

About a quarter to a third of dementia cases can be prevented through the modification of key risk factors including low educational attainment and well known cardiovascular risk factors [23]. Following these findings, the prevalence of dementia has been reported to be declining among older US adults between 2000 and 2012 [24]. However in most regions of the world dementia rates are growing rapidly in relation to population aging [25]. The decline in the USA occurred in those older than 65 years and was related to increased number of years in education [24], despite the age- and sex-adjusted increase in the prevalence of hypertension, diabetes, and obesity in the same observation time. A risk score incorporating common genetic variation outside the APOEε4 locus may improve AD risk prediction and facilitate risk stratification for prevention trials. Future studies are needed to assess how the risk variables interact together to increase an individual's risk of future dementia, also taking into account comorbidities such as diabetes [26]. The field of metabolic studies, including the omics, is particularly promising [27-29] and recent collaborative studies have contributed to identify different profiles [30]. In the absence of effective treatments for dementia a multimodal intervention consisting of diet, exercise, cognitive training and vascular risk monitoring could maintain or even improve cognitive functioning in an at-risk population [31]. Exercise has been shown to enhance neurotrophic factor signaling [32].

The prodromal phase of neurodegenerative disorders with inflammatory features, such as AD, includes mild cognitive impairment (MCI) whose tendency to progress to dementia is not easily captured by a single test [33-39]. This is an area where more studies are needed to validate a set of predictive biochemical, genetic and radiographic determinations [36, 40-42]. Refinements in imaging techniques will help to follow changes from MCI to AD [37, 43]. The role of CSF biomarkers has been evaluated [44] and a consensus reached on its usefulness as a supplement to clinical evaluation, particularly in uncertain and atypical cases [45], but it is not yet recommended as a substitute for neuroimaging [46].

Prevalence of dementias of all types increase with old age, from about 2-3% among those aged 70–75 years to 20–25% among those aged 85 years or more [47]. Taken together for the two most frequent types of dementia (AD and Vascular) [48] vascular risk factors such as T2D, hypertension, dietary fat intake, high cholesterol, and obesity have emerged as the most important determinants [49].

The predisposing factors are being investigated in longitudinal studies as well as in retrospective studies. They reveal a complex picture of interrelated morbidities which need to be assessed with respect to the treatments administered to manage each one. A novel approach to understand AD pathogenic mechanisms is therefore needed. This can generate new models of the dynamic nature of relations among different levels (biochemical, genetic, vascular) and offer new therapeutic candidates which can be targeted by combined treatments and be used to assess disease course. It is in this scenario that the new journal has the potential to contribute to the debate on the ever increasingly complex aspects of AD research and therapy.

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