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Roadmap to Alzheimer's Biomarkers in the Clinic

The biomarker-based diagnosis of Alzheimer's disease. 2—lessons from oncology

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ABSTRACT

Biomarkers for the diagnosis of Alzheimer's disease (AD) are not yet validated for use in clinical settings. We aim to provide a methodological framework for their systematic validation, by reference to that developed for oncology biomarkers. As for this discipline, the steps for the systematic validation of AD biomarkers need to target analytical validity, clinical validity, and clinical utility. However, the premises are different from oncology: the nature of disease (neurodegeneration vs. cancer), the purpose (improve diagnosis in clinically affected vs. screening preclinical individuals), and the target population (mild cognitive impairment patients referring to memory clinics vs. general population) lead to important differences, influencing both the design of validation studies and the use of selected biomarkers. This framework is applied within a wider initiative to assess the current available evidence on the clinical validity of biomarkers for AD, for the final aim to identify gaps and research priorities, and to inform coordinated research efforts boosting AD biomarkers research.

1. From a pathologic to a clinicobiological approach to the diagnosis of AD

The aim of this article is to define a methodological framework for the validation of biomarkers for diagnosing Alzheimer's disease (AD) in people referred to memory clinics or other specialist outpatient service, and meeting current diagnostic criteria of mild cognitive impairment (MCI) (Albert et al., 2011), which includes an important proportion of patients in the prodromal phase of AD (Dubois et al., 2007). Although the definite diagnosis of AD may be posed only after pathologic confirmation, possible or probable AD can be diagnosed assessing the clinical features listed in widely accepted sets of diagnostic criteria (i.e., McKhann et al., 1984, 2011; the 10th edition of the International Classification of Diseases, ICD-10 [WHO - World Health Organization, 2012], and the US Diagnostic and Statistical Manual of Mental Disorders, DSM-5 [APA - American Psychiatric Association, 2013]). In the last

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[1] http://centroalzheimer.it/public/MB/BM-Roadmap/The_Geneva_AD_Biomarker_Roadmap_Task_Force.docx.

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decade, evidence accumulated that the accuracy of the in vivo diagnosis can be improved using assays indicating the presence of the key pathologic hallmarks of AD. These assays of in vivo biological or molecular characteristics of the pathologic process underlying AD may be used as clinical biomarkers because they are associated with the disease status or progression, and may capture biological responses to pharmacologic or nonpharmacologic interventions.

The presence of the main neuropathological AD changes, namely extracellular (amyloid) and intracellular (tau) lesions, synaptic dysfunction, and neuronal death may be identified during the long prodromal phase that precedes the clinical onset of AD. Methods of detection include direct evidence of brain amyloidosis and tau deposits from amyloid (Klunk et al., 2004) and tau ligands uptake at PET imaging (Brier et al., 2016; Johnson et al., 2016; Scholl et al., 2016; Schwarz et al., 2016; Villemagne et al., 2014), or indirect evidence such as the altered concentrations of the Abeta42 and tau proteins in CSF specimens (Blennow et al., 1995; Iqbal and Grundke-Iqbal, 1997). The downstream synaptic dysfunction and loss of brain integrity may be identified using functional (FDG-PET, e.g., temporoparietal hypometabolism; de Leon et al., 1983; McGeer et al., 1986) and structural neuroimaging (MRI). In particular, medial temporal atrophy, assessed either visually (Scheltens et al., 2002) or quantitatively (Boccardi et al., 2015) has great prognostic value, and automated quantification is now accessible to physicians through different services (Tanpitukpongse et al., 2017). Finally, other assays tapping pathophysiological processes (namely, degeneration of the dopaminergic nigrostriatal pathway with ^{123}IMIBG scintigraphy—Treglia and Cason, 2012, and myocardial postganglionic sympathetic dysfunction with ^{123}I-Ioflupane SPECT—Papathanasiou et al., 2012) may be used to exclude non-AD degenerative disorders (e.g., Lewy body dementia). The possibility to detect or exclude pathophysiological processes typical of AD has additional value considering that differential diagnosis is further complicated by the atypical presentations of AD (Dubois et al., 2010; McKhann et al., 2011).

The contribution of these AD biomarkers to improve the accuracy of the clinical diagnosis depends on the demonstration of their analytical validity, which is their ability to detect the key pathological hallmarks of AD and the correlated brain damage and dysfunctions. The available empirical evidence on the analytical and clinical validities of the aforementioned AD biomarkers is presented in the 6 reviews reported in this issue (Cerami et al., 2017; Chiotis et al., 2017; Garibotto et al., 2017; Mattsson et al., 2017; Sonni et al., 2017; Ten Kate et al., 2017). The availability of in vivo measures of AD pathology of proven analytical validity has the transformative potential to provide a diagnosis of AD based on a clinicobiological rather than a clinicopathological basis. Moreover, because the neuropathology underlying AD accumulates gradually over several decades and the insidious onset of the disease reflects the long induction and latency periods (Jack et al., 2013a), the possibility to accurately measure AD-related brain changes in vivo can substantially contribute to the detection of AD at the preclinical stage when future curative treatments might be more efficacious.

1.1. Relevance of early diagnosis

Currently, the ability of the biomarkers alone to predict the clinical expression of AD in not yet symptomatic individuals is not known (Sperling et al., 2011). Together with the lack of disease-modifying treatments, the use of biomarkers for population screening is currently not justified in terms of costs and benefits. On the other hand, improving diagnosis in people with the highest probability of having the disease, at the earliest possible time, is an aim that can and should be reasonably pursued in the short term. This can be done by targeting outpatient clinical settings, where people with a high probability of having AD seek medical advice often before the disease has impacted on autonomous living. The possibility to provide an early diagnosis in this context critically depends on 2 main factors. First, the affected people or their carers must express their concern. This can be negatively impacted by low awareness, limited understanding, and stigma (WHO Dementia Report, 2012) particularly in low- and middle-income countries (Albanese et al., 2011). Second, the health system must respond adequately: such responsiveness can be improved using a biomarker-informed diagnostic approach. Consistent with this context, our effort focuses on the use of biomarkers for detecting AD in symptomatic, including mildly symptomatic, individuals who (or whose caregivers) express concern for their decline. Indeed, this scenario is frequent and has become the norm rather than the exception in high-income countries' memory clinics. Providing an early diagnosis in symptomatic individuals seeking help would respond to an expressed, not proactively elicited concern and would maximize benefits from the available knowledge and resources as to date.

We maintain that early diagnosis is potentially beneficial even in the absence of a disease-modifying drug. First, it provides an explanation for mild symptoms and perceived changes in cognitive function that some people recognize as problematic. Second, early diagnosis would maximize the possibility that interventions that are proven to ameliorate the quality of life of patients and families can be started as early as possible. In fact, early interventions may be beneficial in people at risk (Andrieu et al., 2011; Cesari et al., 2015; de Souto Barreto et al., 2016; Kivipelto et al., 2013; Ngandu et al., 2015) and may favor compression of cognitive morbidity (Langa et al., 2008; Petersen et al., 2005), contributing to delaying disability with considerable savings on direct (e.g., institutionalization) and indirect (e.g., informal caregiving) costs. Moreover, the past failure of AD randomized controlled trials (Winblad et al., 2016) was indeed ascribed, as a possible cause, to the lack of accurate recruitment procedures in confirming the presence of the brain damage that the drug under study was designed to treat or reduce (Mangialasche et al., 2010). Nowadays, biomarker-based diagnosis is being used to inform better study designs, particularly for the selection and inclusion of participants for experimental studies testing potential beneficial effects of interventions targeting specific disease mechanisms. On the clinicaltrials.gov web site, a search using the string "Alzheimer AND anti-amyloid AND phase 3" (January 10, 2017) sorted out 3 nonoverlapping studies, of which one (Solanezumab) includes amyloid positivity at PET or CSF as an inclusion criterion. The same search using "anti-tau" found one study, testing NPT088, which is actually in phase 1 but does use amyloid-PET positivity as an inclusion criterion. This use of biomarkers will definitely increase the power of clinical trials; however, their accuracy will critically influence the appropriateness of subject selection and, thus, the final power of these studies.

1.2. Objective

The aim of this article is to define a methodological framework for the validation of AD diagnostic biomarkers in people referred to a memory clinic or other specialist outpatient service and who meet current MCI diagnostic criteria (Albert et al., 2011). The ultimate goal is to improve the early diagnosis of AD in memory clinics and to operationalize biomarker-based diagnostic criteria originally conceived for research (Albert et al., 2011; Dubois et al., 2014).

2. Methods

2.1. Context of use

Research on AD biomarkers needs to be conducted within a conceptual framework that specifies the purpose of their use, the