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Review

Fluid and imaging biomarkers for Alzheimer's disease: Where we stand and where to head to

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ABSTRACT

There is increasing evidence that a number of potentially informative biomarkers for Alzheimer disease (AD) can improve the accuracy of diagnosing this form of dementia, especially when used as a panel of diagnostic assays and interpreted in the context of neuroimaging and clinical data. Moreover, by combining the power of CSF biomarkers with neuroimaging techniques to visualize Aβ deposits (or neurodegenerative lesions), it might be possible to better identify individuals at greatest risk for developing MCI and converting to AD. The objective of this article was to review recent progress in selected imaging and chemical biomarkers for prediction, early diagnosis and progression of AD. We present our view point of a scenario that places CSF and imaging markers on the verge of general utility based on accuracy levels that already match (or even surpass) current clinical precision.

1. Introduction

Alzheimer's disease (AD) is one of the most common illnesses of later life and currently affects 35.6 million worldwide, with such number expected to increase to 65.7 million people in 2030 and to 115.4 million in 2050 (Organization WH, 2012). At present, AD cannot be diagnosed until a dementia phenotype has been clinically established (American Psychiatric Association APA, 2013) and there are no treatments to change the course of this progressive neurodegenerative disorder (Services USDoHaH, 2015a; Blennow et al., 2015). Growing evidence suggests that cellular and brain changes associated with the disease begin years — even decades — before people first show clinical symptoms of memory loss or cognitive/behavioral difficulties (Scheltens et al., 2016; Jack Jr et al., 2013; Lewczuk et al., 2015; Counts et al., 2017). Mild cognitive impairment (MCI) usually precedes the AD-related cognitive dysfunctions, despite not all MCI cases evolve into AD (Lewczuk et al., 2015). MCI individuals display increased risk of developing AD within 3–5 years, and almost 45% of all MCI patients evolving to AD within 5 years (Shaw et al., 2007; Skovronsky et al., 2006). Researchers are increasingly investigating biomarkers for AD — specific proteins in blood or cerebrospinal fluid (CSF) as well as imaging of brain structures and functions (Zafari et al., 2015) — to identify changes which could measure the risk for AD onset, mostly in MCI context but even in symptom-free people, in pursue of strategies to effectively diagnose and treat as soon as possible, or provide the opportunity to intervene before major neuronal and synaptic losses occur. Large-scaled, controlled multicenter trials on biomarkers are currently being conducted in an attempt to develop and validate core feasible candidate elements, mostly related to structural and functional imaging and neurochemistry (Ashton et al., 2015; Prestia et al., 2015).

Although the clinical symptoms of AD are frequently diagnosed at older ages, such degenerative processes start many years before the clinical onset of the disease (Jack et al., 2010). The presymptomatic detection of AD is crucial, and could facilitate implementation of early and efficient treatments (pharmacological and non-pharmacological) to modify the course of the natural history of this important, life-threatening disorder. Besides an important role in diagnostics, biomarkers can also provide insight into the AD pathogenesis.

The diagnosis of late-onset AD based solely on clinical symptoms has shortcomings, particularly in the prodromal phase (Services USDoHaH, 2015a). This difficulty is reflected in the modestly accurate clinical method for AD diagnosis existent to date which cannot rely on fairly informative and accessible biomarkers. Sensitivities of the classical clinical approach have been reported to range from 71% to 88% whereas specificities varies from 44% to 71% (Beach et al., 2012), given how different dementia with very distinct histopathological and

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pathophysiological properties resemble each other at first glance. It is expected that accuracy of any clinically-based diagnosis is probably even lower in the very early stages of a disease (*i.e.*, in patients with prodromal AD), preventing the disease from being properly addressed and treated. The major pathological hallmarks of the late-onset AD are the loss of neurons, occurrence of extracellular senile plaques as well as intracellular neurofibrillary tangles (NFT) (American Psychiatric Association APA, 2013; Anoop et al., 2010). Core CSF biomarkers for AD are the amyloid beta peptides Aβ, total tau protein and phosphorylated tau (Sutphen et al., 2015; Babic et al., 2014). Beyond fluid biomarkers, imaging tests to determine the likelihood of AD pathology, the staging of preclinical AD and the progression from prodromal to clinical AD (Alexopoulos et al., 2016; Guo et al., 2013; Sperling et al., 2011) are under development by means of positron emission tomography (PET) for amyloid deposits, by magnetic resonance imaging (MRI) for mesial temporal lobe (MTL) atrophy and by radiolabeled fluorodeoxyglucose (FDG) - PET", since FDG stands for fluorodeoxyglucose alone, and not for its radiolabeled form as indicated in the present form for tempoparietal/precuneus hypometabolism or hypoperfusion.

Based on the potential of these CSF and imaging markers in accurately estimating the risk of and/or detecting AD and MCI (Babic et al., 2014), the authors summarize their understanding on the most importantly studied biomarkers that are likely to advance the field of AD diagnosis in forthcoming years.

2. Biomarkers

2.1. Chemical established biomarkers

2.1.1. Amyloid beta peptides

One of the major pathological features of AD consists in the presence of senile plaques and a reasonable amount of evidence demonstrates that $A\beta_{42}$ levels are decreased in the CSF of AD patients (Babic et al., 2014; Frank et al., 2003; Pannee et al., 2016; Grimmer et al., 2009). About 20 studies (2000 patients and controls) have been conducted so far showing a reduction of $A\beta_{42}$ by around 50% in AD patients compared to age-matched, nondemented controls, with diagnostic sensitivity and specificity levels ranging between 80% and 90% (Blennow & Hampel, 2003). It is not clear why $A\beta_{42}$ titers are reduced in AD, but deposition of the peptide ("amyloid sinks") in plaques is considered the underlying basis for such phenomenon. In favor to a usefulness of this marker, studies have demonstrated an inverse correlation between $A\beta_{42}$ levels in the CSF of AD patients and the number of plaques both at autopsy (Strozyk et al., 2003) an *in vivo* (Grimmer et al., 2009). Also, it was recently shown that subjects with the greatest positive signals in amyloid positron emission tomography (PET) scans using the Pittsburgh Compound B (PIB) had the lowest $A\beta_{42}$ values in CSF of patients with MCI (Forsberg et al., 2008). Having that in mind, total $A\beta_{42}$ in the CSF has high potential as a biomarker for plaque burden and prognosis for neurodegeneration and may provide useful clue for preclinical AD (Anoop et al., 2010; Mo et al., 2015). A more precise AD biomarker than $A\beta_{42}$ alone appears to be the $A\beta_{42}/A\beta_{40}$ ratio, even though $A\beta_{40}$ is slightly increased or unchanged in the CSF of AD patients (Pannee et al., 2016).

2.1.2. Total tau protein

The protein tau is an intracellular protein which maintains the stability of microtubules in neurons. Plenty of studies conducted with patients and control groups have all demonstrated an increase in the concentration of total tau (t-tau) in AD patients by approximately 300% compared to nondemented elderly subjects (Blennow et al., 2015), whereas a systematic increase in the concentration with age was observed in the control groups (Burger nee Buch et al., 1999). Augmented levels of tau protein predict MCI conversion to AD with 83% sensitivity and 90% specificity (Blennow & Hampel, 2003; Struyfs et al., 2014). For this reason, CSF t-tau seems a more dynamic biomarker, which reflects the intensity of both acute neuronal damage and chronic neuronal degeneration in the brain, with high levels of CSF t-tau associated with faster progression from MCI to AD, more rapid cognitive decline and higher mortality rate among AD patients (Blennow et al., 2015). Both t-tau and $A\beta_{42}$ are significantly altered in MCI subjects who are at increased risk of AD over time (Hampel et al., 2004).

2.1.3. Hyperphosphorylated tau protein

In AD patients, tau protein is present in a pathologic, hyperphosphorylated form, and several experimental studies suggest that formation of neurofibrillary tangles (NFT) constitutes a downstream phenomenon in AD pathophysiology (Ritchie et al., 2014). In this disorder, tau becomes hyperphosphorylated (p-tau) and gets dissociated from microtubule to subsequently polymerize into insoluble paired helical filaments (PHF) that eventually contributes to the formation of neurofibrillary tangles. NFT formation and neuronal degradation is an essential part of AD pathology (Tang et al., 2014). Several studies also assessed CSF p-tau as potential biomarkers for AD (Pascoal et al., 2016; Olsson et al., 2016). Experimental evidences of high CSF concentrations of p-tau in selected patients with a very typical AD phenotype have suggested that p-tau is not a simple marker of axonal damage and neuronal degeneration, as is shown for t-tau. Instead, p-tau is more closely related to an AD pathology and, accordingly, to the formation of NFT (Anoop et al., 2010). P-tau is a more specific marker for AD and has proven its value for differential dementia diagnosis (Struyfs et al., 2014).

In MCI subjects, high CSF p-tau concentrations correlated with a decline in cognitive performance and conversion to AD (Smailagic et al., 2015). An European multicenter trial on CSF p-tau among MCI subjects has shown that abnormally high p-tau levels predicts AD in this risk group, producing stable and consistent evidence throughout multiple centers. In that study, p-tau proved to be a powerful predictor of AD among MCI subjects even in short-term conditions as 1 or 2 years of follow up (Hampel et al., 2008). In line, the high negative predictive value of p-tau of approximately 90% appears to be particularly significant (Mitchell & Brindle, 2003), with barely no patients with normal p-tau titers evolving into an AD phenotype. This result is particularly promising regarding clinical use of p-tau to inform patients as early as possible.

Also seen in some 2-years follow up studies (Papaliagkas, 2013; Brys et al., 2009), p-tau is considered to be an accurate marker of MCI conversion to AD, with 80% specificity and 80% total diagnostic accuracy. Moreover, it shows 90.2% sensitivity and 80.0% specificity in discriminating between AD and all non-AD disorders (Papaliagkas, 2013). Altogether, p-tau shows to be the strongest predictor of the decline from MCI to AD (Tang et al., 2014; Brys et al., 2009).

2.2. Neuroimaging

A very important progress in human brain research was the development of imaging techniques, which allows the visualization of brain characteristics *in vivo*, providing information about chronological and spatial evolution of disease pathology (Weiner et al., 2013). Functional and molecular neuroimaging provide insights into brain structure and physiology and can detect specific proteins and protein aggregates associated with AD in the brain (Zhang et al., 2014). In AD, structural imaging data from computerized tomography (CT) and magnetic resonance imaging (MRI) show a progressive cerebral atrophy as a probable reflection of dendritic and neuronal loss, a neurodegenerative hallmark of the disease. Another type of information can be acquired using radioligands to detect molecules of interest using positron emission tomography (PET) imaging. In AD, the most applied imaging modalities so far are the ones measuring brain metabolism ($[^{18}F]$fluorodeoxyglucose ($[^{18}F]$FDG)) and amyloid load ($[^{18}F]$florbetapir and $[^{11}C]$Pittsburg Compound B ($[^{11}C]$PIB)).