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COMMENTARY

Is it time for biomarker-based diagnostic criteria for prodromal Alzheimer's disease?

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Abstract

Drug candidates targeting amyloid-β (Aβ) pathology in Alzheimer's disease are in different phases of clinical trials. These treatments will probably be most effective in the earlier stages of the disease, before neurodegeneration is too severe, but at the same time symptoms are vague and the clinical diagnosis is difficult. Recent research advances have resulted in promising biomarkers, including cerebrospinal fluid analyses for tau and Aβ, magnetic resonance imaging measurement of atrophy, and positron emission tomography imaging of glucose metabolism and Aβ pathology, which allow identification of prodromal Alzheimer's disease. More details are needed, however, on how these biomarkers can be standardized, to allow a general implementation in the clinical routine diagnostic work-up of patients with cognitive disturbances.

It is now more than 25 years since the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now the Alzheimer's Association) established the most commonly used diagnostic criteria for Alzheimer's disease (AD) [1]. These criteria require that the patient is demented before a diagnosis of AD can be made. We now know, however, that dementia represents a late stage of AD and that AD-specific neurodegeneration starts many years earlier. Disease-modifying drugs that attack primary pathogenic processes underlying AD will probably be most effective in the earlier stages of the disease, before plaque and tangle load and neurodegeneration have become too severe.

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If we want to do something substantial about the prospects of AD patients in the near future, we need to develop diagnostic algorithms that recognize pre-dementia stages of the disease. This has become possible thanks to brain imaging and cerebrospinal fluid (CSF) analyses that predict AD with dementia in patients with mild cognitive impairment [2-4]. Accordingly, new research criteria for the diagnosis have been proposed that capture both the prodromal and the more advanced dementia stages of the disease in the same diagnostic framework [5]. In the present article, we discuss what is needed before this type of criteria can be implemented in the clinical routine diagnostic work-up of patients with cognitive disturbances.

Validated biomarkers for Alzheimer's disease

CSF levels of total tau reflect cortical axonal degeneration, levels of phospho-tau reflect tangle pathology and levels of the 42-amino-acid isoform of amyloid β (Aβ42) reflect brain amyloid pathology [2]. Magnetic resonance imaging (MRI) of hippocampal atrophy gauges progression of the neurodegeneration in a manner that correlates well with both neuropathological measures of tangle load and cognitive symptoms [3]. 2[^{18}F]-Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) allows for the assessment of the glucose metabolism rate in specific brain regions and can detect metabolic dysfunctions in brain regions affected by AD also in pre-dementia stages [4]. Amyloid plaques in the living human brain can be visualized using amyloid-binding PET tracers such as Pittsburgh Compound B (PIB) [4]. Marked PIB retention is found in AD patients in areas of the brain known to contain large amounts of Aβ plaques.

When do the biomarkers turn positive?

In a recent review, Jack and coworkers condense the AD biomarker literature to model the sequence of pathological events in AD [6]. The first biomarker change to occur in AD is probably the lowering of the CSF Aβ42, reflecting the formation of oligomers and loose aggregates of Aβ in the brain. This change is followed by PIB-PET positivity as a sign of accumulation of fibrillar Aβ in the brain. Aβ oligomerization, or an unknown molecular

change, induces metabolic dysfunction – seen as lowered glucose metabolism on FDG-PET – and axonal degeneration and hyperphosphorylation of tau – seen as elevations in total tau and phospho-tau concentrations in the CSF. Eventually, the axonal and neuronal loss in specific brain regions is manifested as reduced MRI volumes of, for example, the hippocampus, which parallels cognitive decline. The model is supported by a vast body of literature and suggests that most biomarkers listed above are positive in the mild cognitive impairment stage of AD and that amyloid-related biomarkers are the most promising antecedent biomarkers for AD [6].

What is the diagnostic performance of these biomarkers?

Sensitivity and specificity figures for the different bio-markers vary between studies but tend to be above 80% for distinguishing AD patients from cognitive normal controls and for identifying incipient AD in the mild cognitive impairment stage of the disease, at least in standardized monocenter studies [2-4]. Only a few of the biomarkers have as yet undergone testing in large multicenter settings.

Why are Alzheimer's disease biomarkers not 100% specific?

Currently available biomarkers do not show full-proof diagnostic accuracy. Except for technical shortcomings with the biomarkers, however, there are several funda-mental reasons why 100% sensitive and specific bio-markers for AD are an unreachable goal. Most biomarker studies are based on clinically diagnosed cases, which introduces a relatively large percentage of misdiagnosis [7]. There is also a large overlap in pathology between AD and other dementias, such as Lewy body dementia and vascular dementia [8,9]. This overlap in pathology essentially precludes the possibility of finding biomarkers that have close to 100% sensitivity and specificity for AD. One way out of this conundrum might be to reconsider the terminology. Perhaps we should stop using the term AD biomarkers and instead acknowledge that the biomarkers reflect distinct pathogenic or pathologic processes; for example, amyloid retention in the brain and degeneration of nonmyelinated cortical axons. These changes, especially in combination, are frequently seen in AD but may also be present in other neurodegenerative disorders, especially in isolation.

It is known that a significant percentage of non-demented older people have enough plaques and tangles to warrant a neuropathological diagnosis of AD [10]. Recent biomarker studies corroborate this finding. For example, a relatively large portion of cognitively normal older people have CSF Aβ42 values or PIB-PET binding similar to that found in AD cases [2-4]. These findings

raise the question of whether the term normal aging has to be redefined. Longitudinal studies will tell us whether these individuals do have preclinical AD, or whether silent AD pathology is part of the normal aging process.

Which biomarkers should be used and how?

More detailed guidelines on how biomarkers should be implemented in the diagnostic procedure for early AD are needed for them to be used in clinical routine. Notably, these guidelines have to be down-to-earth to allow for general implementation. A large number of unresolved issues need to be settled.

Assessment of memory

There is to date no consensus on which tests should be used to identify impairment in episodic memory and other cognitive domains beyond what is expected due to normal aging [11]. Further, a major challenge will be to determine cut-off points that can be generally applied to identify patients with cognitive dysfunction, since a cut-off point set in one population does not necessarily apply to populations with other ethnic or socioeconomic characteristics.

Biochemical markers in the cerebrospinal fluid

Although assays for measurement of tau and Aβ in CSF have been well validated and the biological variability for these biomarkers is low [2], there is a variation in bio-marker levels in reports from different research centers, even when using the same assay [12]. Moreover, there is no accepted gold standard method and no consensus on what assays are to be used. A first study comparing CSF biomarker levels between laboratories found excellent within-laboratory variation, but a large variation between centers [13]. Similar results were reported in a large multicenter study [14]. This variation complicates multicenter research studies and trials, and also precludes the introduction of generally applicable cut-off levels. To help deal with this problem, a global quality control program for CSF biomarkers was recently launched [12].

Structural magnetic resonance imaging

The utility of structural imaging in diagnostic guidelines will be increased by standardization of acquisition and analysis methods [3]. Which is the region of interest with regards to AD-type brain atrophy measured on MRI? Which methods and what cut-off points should be used to distinguish age-related brain atrophy from atrophy in AD?

Positron emission tomography

Similar standardization issues that apply to MRI also apply to PET imaging of cerebral Aβ aggregation and glucose metabolism. Where in the brain should amyloid retention be quantified using amyloid PET? Which of the

different radioligands to label amyloid plaques should be used? Where in the brain should we monitor cerebral glucose metabolism using FDG-PET, and should we focus on different regions in different disease stages?

How about availability and costs?

For the implementation of these biomarkers in a diagnostic algorithm, availability and financial considerations may be of importance. Amyloid PET is at present only available in highly specialized centers. In Sweden, the approximate cost is $200 for CSF biomarkers (combined analysis of total tau, phospho-tau and Aβ42), $500 for structural MRI and $5,000 for amyloid PET – figures that probably vary considerably between countries.

How should we move forward?

There is an enormous amount of literature showing good or excellent diagnostic performance of several biomarkers reflecting different facets of the disease process in AD. We have unprecedented possibilities to phenotype our patients. We think the time is ripe to boldly develop the biomarker-based research criteria proposed by Dubois and coworkers [5] into a detailed, practical and feasible diagnostic algorithm that will be applicable in clinics worldwide. It is easy to predict that this will be a challenging process. The proposed algorithm would require evaluation in a longitudinal clinical multicenter study of patients with memory problems to assess its diagnostic (or strictly speaking as it is now, predictive) accuracy against postconversion clinical dementia diagnoses and, whenever possible, to neuropathological findings before general implementation in the clinic. Such an evaluation will require some significant period of time. It is in the best interest of all who wish to develop better therapeutic paradigms for this devastating disease that this process be started now.

Abbreviations

Aβ, amyloid β; AD, Alzheimer's disease; CSF, cerebrospinal fluid; FDG, 2[¹⁸F]-fluoro-2-deoxy-ᴅ-glucose; MRI, magnetic resonance imaging; PET, positron emission tomography; PIB, Pittsburgh Compound B.

Competing interests

KB has served on an advisory board for Innogenetics, Belgium. The authors declare no other competing interests.

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