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Critical Assessment of the Status of Biomarkers for Alzheimer's disease

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Abstract

Objective: We undertook a critical analysis of the status of the progress in the development of biomarkers for the detection of Alzheimer's disease (AD).

Methods: Biomarker studies involving imaging, metabolomics, lipidomics, proteomics, transcriptomics and microRNAs were assessed from publications between 2004 and 2014.

Results: Extensive efforts have been applied to the development of minimally invasive and inexpensive assays for the early detection of AD. However, the failure to replicate findings between laboratories has presented a significant challenge in validating assays for clinical use. Larger scale studies and collaborations are required to standardize sample collection and storage, analytical methodology, and to control for heterogeneity in the AD patient population.

Conclusions: Since cognitive testing cannot detect the pre-symptomatic stages of AD, validated biomarkers are essential for advancing both AD research and clinical practice. Despite intensive research over the last 10 years, there currently are no validated biomarkers for the early detection of AD.

Introduction

The clinical diagnosis of Alzheimer's disease (AD) involves elimination of alternate potential causes for cognitive decline, with the diagnosis ultimately requiring neuropathological confirmation at autopsy. However, current research efforts in AD have demonstrated that historical assumptions are not valid and that heterogeneity in clinically defined AD populations is more complex than was anticipated. This is best exemplified by elderly individuals who demonstrate limited cognitive deficit but at autopsy possess a neuropathology burden (plaques and tangles) that would result in a diagnosis of AD [1-5]. These individuals have been termed non-demented with AD neuropathology or NDAN [4,5]. The mirror image elderly population encompasses individuals demonstrating poor memory and executive functions, with neurodegenerative abnormalities (e.g. cortical thinning), but in the absence of amyloid deposition [6,7].

These data clearly indicate that historical post-*mortem* definition of AD need reassessment and that heterogeneity in the clinically diagnosed AD patient population offers challenges to the development of *ante-mortem* biomarkers to detect and monitor the progress of AD and for the development of therapeutic interventions for subpopulations with different disease etiologies.

Improvements in the ability to more accurately define patient subpopulations in AD will ultimately lead to the development of therapeutic interventions and individualized patient care. This lofty goal will only be reached by integrating cognitive evaluation, imaging, and biomarkers as well as collaboration between academic researchers, government, and the pharmaceutical industry. An excellent example of this approach involved evaluation of the heterogeneity in mild cognitive impairment (MCI) subjects utilizing cognitive testing, imaging of hippocampal and ventricular volumes, imaging of white matter hyperintensities (WMH), and CSF tau and amyloid-beta (Aβ) [8].

Cognitive Testing

Dementia diagnosis in primary medical care remains a challenge despite advances in the development of brief cognitive screening instruments with decreased susceptibility to cultural and educational biases [9,10]. To increase our ability for the early detection of the disease process in AD, intense research efforts have been undertaken to characterize MCI and pre-MCI [11]. Impairment in episodic memory has been shown to be a reliable index of the likelihood of progression from MCI to AD [12]. Other cognitive domains that demonstrate impairments include executive function, language, attention, and visuospatial skills [11-13]. However, there is significant heterogeneity in the expression of these impairments. For example, it has recently been demonstrated that patients demonstrating greater amnestic deficits than executive dysfunction have greater odds of having hypertension and the APOEε4 allele than subjects where executive dysfunction predominates [14].

In summary, a number of new cognitive instruments are being used in AD research in combination with imaging and biomarkers. However, there remains a large divide in advancing reliable testing paradigms into primary care.

Imaging

Advances in the resolution of imaging techniques have made possible a number of advances in the evaluation of brain structural changes in MCI and AD. Longitudinal MRI has demonstrated progressive brain atrophy of 1 to 3% per year in AD [15], with detection approximately 3 years prior to a clinical diagnosis of AD. Also of note is that brain atrophy is less in cognitively normal individuals (NDAN) who at autopsy demonstrate a high burden of AD pathology (Braak stage V or VI) [1]. The limitations of this imaging approach are that brain atrophy is not unique to AD, the rates of atrophy are small with large error estimates, brain shrinkage is not an early disease process,

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and the technology is not simple or inexpensive. Studies combining MRI volumetric data with ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scans have indicated that hypo metabolism generally precedes atrophy in MCI patients and is also detected in brain areas that subsequently demonstrate little atrophy [16]. As with MRI, this approach is limited by expense, availability of PET facilities, and determination of the sensitivity of this approach for early detection requires expanded investigation to larger clinical populations.

In addition to brain atrophy, diffusion tensor imaging (DTI) has detected decreased white matter integrity in MCI and AD, independent of cortical thinning [17,18]. A major issue that still remains to be resolved is the relative contributions of altered oligodendroglial function and cerebral small vessel disease to the white matter findings in AD. In the case of small vessel disease, cerebral microbleeds are evident in approximately 40% of AD patients, 24% of MCI patients, and 18% of age-matched controls [19,20]. These data clearly indicate that cerebral vessel dysfunction contributes to the heterogeneity of clinical populations utilized in the search for AD biomarkers.

Brain amyloid imaging has been made possible by the introduction of PET amyloid ligands [21]. While PET amyloid imaging has been approved by the FDA, the major concern with this biomarker relates to its specificity and therefore utility in clinical practice. There are a number of issues related to the issue of specificity. First, PET amyloid ligand imaging has shown that a significant number of cognitively normal elderly have amyloid-beta (Aβ) deposition in the brain, with deposition increasing over time [22]. Second, significant AD pathology, including extensive amyloid deposition, has been reported for a substantial number of cognitively normal elderly at autopsy [2,3]. Third, there appear to be a significant number of cognitively normal elderly which possess features of neurodegeneration (cortical atrophy and white matter lesions) but no increase in Aβdeposition as reflected by PET amyloid ligand imaging [6,23]. Fourth, large-scale phase III clinical trials have revealed that 10 to 35% of clinically diagnosed AD patients have no Aβ deposition as detected by PET imaging [24]. Fifth, while amyloid lowering agents are effective in reversing pathology and cognitive decline in amyloid mouse models they all have failed in the clinic [25]. These data suggest that while PET amyloid ligand imaging may be a tool in the evaluation of AD patients, it is not a test that will stand alone without other biomarkers.

Proteomics

Extensive research has been directed to identify and validate cerebrospinal fluid (CSF) biomarkers of AD. The universal conclusion is that a combination of biomarkers is superior to any individual biomarker. While a number of algorithms have been proposed by various laboratories, a simple ratio of higher total tau or phosphorylated tau (p-tau) to lower amyloid-beta (Aβ42) appears to detect MCI patients who convert to AD [26]. However, it is important to remember that increased levels of tau or p-tau are a non-specific marker of neurodegeneration associated with a diversity of biological processes. Similarly, decrements in CSF Aβ42 are not specific to AD. These decrements also are found in vascular dementia, corticobasal degeneration, frontotemporal lobar degeneration, Lewy body dementia, and cerebral amyloid angiopathy [27].

Evaluation of plasma proteomics in MCI and AD is at an earlier stage of maturity. Current methodology is limited by poor reproducibility such that some proteins can be statistically different in opposite directions on replication [28,29].

Metabolomics

Metabolomics studies have revealed potential alterations in a number of amino acids and metabolites of intermediary metabolism [30-33]. However, the failure to replicate findings between laboratories may well relate to labiality of many of these metabolites and demands further investigation.

Lipidomics

Lipidomics studies in AD have mainly focused on glycerophospholipids and sphingolipids [34]. The most remarkable glycerophospholipid alteration involves decrements in choline and ethanolamine plasmalogens in brain [35], liver [36] and plasma [37,38] from AD patients. However, more recent evaluations of plasma [32,39] and brain [40-42] plasmalogens from MCI patients have demonstrated that alterations in these lipids do not occur early in the disease process, thereby limiting their value as *ante-mortem* biomarkers. Recent publication of a panel of 10 plasma lipids as a potential biomarker of antecedent memory impairment is limited by the fact that the means of all 10 lipids in the MCI groups were within the error bars of the age-matched controls [30].

Data obtained from sphingolipid metabolism in AD are more controversial. Large decrements in white matter levels of sulfatides and associated increases in ceramides have been reported as an early lipid change in AD [41]. However, replication of these studies by other laboratories has reported more modest alterations in these oligodendroglial lipids in AD brain [40-43].

Similarly analysis of plasma sphingolipids has generated variable data. While elevated ceramides have been reported for AD plasma [44], these findings were not replicated with lower levels of ceramides measured in MCI plasma [45]. Decrements in sphingomyelins also were observed in MCI [45] and AD [45] plasma but contradictory data also has been reported [38].

Other lipid biomarkers of potential interest include desmosterol and diacylglycerols (DAG). Decreased levels of desmosterolin plasma and CSF [46] in AD patients suggest that cholesterol metabolism is altered in the disease process. However, contradictory data also has been published [47].

Increases in the levels of DAG have been reported both for AD cortex [40,42,43] and plasma [38,39]. Since DAG serve as mediators of signal transduction and as precursors to diverse families of structural glycero- and glycerophospho-lipids, these findings need wider validation, particularly since increases were greatest in the plasma [39] and brains [42] of MCI patients.

Transcriptomics

Altered RNA expression in AD blood has been demonstrated for a number of genes, some overlapping with changes in AD brain [48]. These data require further validation by other groups and investigation in MCI patients to determine their possible utility as

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AD biomarkers.

MicroRNA (miR)

miRs are present in biofluids and offer a potential source of novel biomarkers. Recent research has demonstrated increased circulating levels of the miR-132 (miR-128, miR-132, miR-874) and miR-134 (miR-134, miR-323, miR382) families in MCI plasma [49] and AD plasma [50]. The utility of miR biomarkers requires further validation based on the complexity of miR regulatory networks with a single miR possessing hundreds of potential gene targets.

Summary

Biomarker research in dementia is moving forward at a rapid pace. With investments in standardization of methods and enlarged clinical collaborations, biomarkers of clinical utility will become available within a decade.

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