알츠하이머 병의 바이오 마커들에 대한 최신 정보

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Dementia: Biomarkers in Alzheimer Disease

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Alzheimer's disease (AD) is the most common cause of dementia and a progressive neurodegenerative disease including almost one-half of the population aged > 85 years (43%). Neuron loss and the pathologic changes in AD can be detected 15 years before dementia symptom onset. The current clinical diagnosis of AD is applied to a patient to have dementia before a diagnosis can be made, and is largely based on the exclusion of other disorders. Therefore, the identification of the AD biomarkers is important in order to diagnose individuals who are in the early stages of AD, assess whether asymptomatic individuals have the condition, and predict the outcomes of such individuals. Traditional core AD biomarkers are usually divided into cerebrospinal fluid (CSF) (e.g. $A\beta_{42}$, p-tau and t-tau) and neuroimaging (e.g. Magnetic Resonance Imaging and Positron Emission Tomography). This article presents updates on some of the recent advances in AD biomarkers that have demonstrated results and presents updates on some of the current challenges.

Key Words: Alzheimer's disease, Biomarker, Cerebrospinal fluid, Neuroimaging, Diagnosis, Prognosis

Introduction

Since Alois Alzheimer had firstly reported the dementia, Alzheimer's disease (AD) has been the most common form of dementia and accounts for 50-60% of all dementia cases.[1] The flow of many studies in AD has been moving from the diagnosis when it shows clinical features to the diagnosis of early dementia[2] or mild cognitive impairment (MCI),[3] even its early preclinical stages.[4]

Although a probable diagnosis of AD can be established with a confidence of 〉90%,[5] based on clinical criteria, the addition of biomarkers to the diagnostic criteria for AD may facilitate an early diagnosis, and may increase the sensitivity and specificity of both the clinical diagnostic and prognostic capabilities.[6] However, there are great challenges to discover novel biomarkers with high sensitivity and specificity for AD.

Herein, this article review discussions of the newly updated biomarkers in AD as well as traditional core biomarkers as clinical and diagnostic tools.

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Definition and classification of biomarkers

Biomarkers, by definition, are objective, quantifiable characteristics of biological processes.[7]

Many unique purposes of biomarkers include diagnosis confirmation of diagnoses, monitoring treatment effects or disease progression, and prediction of clinical outcomes.[8]

An ideal biomarkers in AD would be as follows; first, they have clear cutoff values for biomarker positivity, second, they diagnose preclinical AD and reflect the different stages of the disease throughout its course; third, they

distinguish AD from other types of dementia, such as mild cognitive impairment (MCI), or mixed forms of dementia, such as vascular dementia (VD), frontotemporal dementia (FTD), or dementia with Lewy bodies (DLB);[5] and fourth, they are simple and not costly, such as might be afforded by a blood test.[6]

Biomarkers can be classified into molecular biomarkers and imaging biomarkers (Computer Tomography, CT; Positron Emission Tomography, PET; Single Photon Emission Computed Tomography, SPECT; and Magnetic Resonance Imaging, MRI).[9] In general, molecular biomarkers refer to nonimaging biomarkers with biophysical properties by a measurement of biological samples such as plasma, serum, cerebrospinal fluid (CSF), bronchoalveolar lavage and biopsy.[9]

Imaging biomarkers capture broad changes of AD neuropathology, from brain size and structure to the presence of protein aggregation.[6] Imaging biomarkers can be noninvasive (MRI) or moderately invasive (PET or SPECT) based on the modality used. A particular advantage for imaging biomarkers is the continual improvement of equipment/software and discovery of new radioimaging ligands, however, interlab standardization can be difficult because of the use of different makes and models of scanners, each with their own idiosyncrasies.[10]

Molecular biomarkers in AD

1. CSF

Although lumbar puncture (LP) is somewhat a more invasive procedure, CSF is considered as an ideal source for biomarkers in AD. It directly interacts with the extracellular space in the brain, thus potentially reflecting the associated biochemical/pathologic changes.[6]

Three proteins (amyloid-β, $A\beta_{42}$; total-tau, t-tau; phosphorylated forms of tau, p-tau), which are the major protein constituents of the hallmark pathological features of AD, are typically considered the gold standards for AD CSF biomarkers.[11] These proteins are major components of amyloid plaques (APs) and neurofibrillary tangles (NFTs), respectively.[6]

1.1 Amyloid-β (Aβ42)

$A\beta_{42}$ is a 42 amino acid peptide cleaved from the large amyloid-precusor protein (APP) by the sequential activities of α-secretase and γ-secretase enzymes, and it aggregates in the brain through the processing of amyloidogenic pathways. The mean concentration of $A\beta^4{}_{42}$ in the CSF is significantly reduced by about 50% in subjects with AD relative to age-matched controls.[12] Low CSF $A\beta_{42}$ is useful as a marker that predicts future clinical disease progression and rate of cognitive decline, especially in the early clinical stages of the disease.[13] This phenomenon results from deposition of $A\beta_{42}$ in APs, preventing its transit from the brain into the CSF.[5] It has been proved in many studies, which CSF Aβ42 levels correlate inversely with APs load in the brain as determined by postmortem histology[14] and concomitant in vivo plaque measurement using amyloid imaging.[15] A cut-off value of internationally established CSF $A\beta_{42}$ in AD compared to controls is less than 500 pg/ml.[5]

CSF $A\beta_{42}$ alone is less useful in differentiating AD from other dementias, because low levels have also been documented in patients with FTD, VD, and LBD.[4] It possibly suggests the concomitant presence of fibrillar Aβ deposits in many of these patients.[4] In addition, CSF $A\beta_{42}$ does not correlate well with disease duration or severity.[4] This is consistent with results from ^{11}C-labeled Pittsburgh Compound B (^{11}C-PIB) studies[16] or the hypothetical model of dynamic biomarkers for AD pathology[17] showing that amyloid retention does not change appreciably during the symptomatic stages of AD.[18]

Unlike CSF $A\beta_{42}$, CSF $A\beta_{40}$ levels are not different in individuals with AD compared with controls.[5] CSF $A\beta_{40}$ has recently been shown to be decreased in a subset of subjects with cerebral amyloid angiopathy (CAA).[19] However, because CSF $A\beta_{42}$ alone is not a sufficient biomarker for AD diagnosis and prognosis,[20] it has been proposed that measurement of the $A\beta_{42}/A\beta_{40}$ ratio might be superior to $A\beta_{42}$ alone, even in the early stages of disease.[21]

1.2 Tau

Tau is a intraneuronal inclusions of the microtubule-associated protein,[5] wherein its primary function seems to be regulation of microtubule stability within the axon.[6] In AD, hyperphosphorylated tau (p-tau) is a major component of the paired helical filaments that constitutes neurofibrillary tangles (NFTs) that are present in neuronal cell bodies.[4]

1.2.1 Total-tau (t-tau)

Tau is normally released by neurons in the absence of cell death.[6] High levels of tau in CSF may reflect neuronal damage, and it can be transiently increased after acute neuronal injury such as with stroke and traumatic brain injuries.[22] Levels of t-tau in the CSF can increase with age in healthy controls,[5] however, the concentration of total tau (t-tau) significantly increases approximately 2-3-fold in AD compared with nondemented elderly subjects with a cut off of 〉600 pg/ml.[5,23] Elevation of CSF t-tau differentiates AD from nondemented, age-matched elderly with a sensitivity and specificity of approximately 90%.[12] Tau levels might also be a prognostic marker with a good predictive validity for conversion from MCI to AD.[24] If cognitively normal individuals show evidence of amyloid deposition and an elevation in t-tau, they are likely to have preclinical AD.[25] However, because t-tau elevation can be seen in other neurodegenerative diseases,[18] the utility of t-tau alone in the differential diagnosis of AD is potentially limited.[26] Also tau levels remain relatively stable throughout the clinically symptomatic period of AD, thus they do not correlate well with dementia severity.[18]

1.2.2 Phosphorylated tau (p-tau)

Abnormal tau phosphorylation is present in NFTs and has been investigated as a marker of

AD pathology.[4] CSF p-tau results in a lack of function and axonal transport dysfunction.[5] In contrast to t-tau, p-tau does not appear to be increased secondary to acute brain injury, further adding to its diagnostic specificity.[4]

The different phosphorylation sites of p-tau,[27] p-tau$_{181}$,[28] p-tau$_{231\text{-}235}$, or p-tau$_{396\text{-}404}$[29] offer at least equivalent diagnostic utility for AD, especially in early diagnosis, as compared with total tau.[4] Three different phosphorylation sites of tau such as p-tau$_{181 \text{ and } 231}$ are equally effective in differentiating AD from nondemented controls.[4] CSF p-tau$_{181}$ is significantly enhanced in AD and MCI,[30] with a cut-off of 〉60 pg/ml,[5] and it improves the differentiation between AD and DLB.[31] Levels of p-tau$_{231}$ in CSF are associated with disease progression in AD.[32] CSF p-tau$_{231}$ may also provide diagnostic specificity for AD and may improve the differentiation between AD and FTD.[33] CSF p-tau$_{396\text{ - }404}$ and the ratio of p-tau$_{396\text{- }404}$/t-tau have been differentiated AD from VD in a study.[29] CSF p-tau$_{181}$ and p-tau$_{231}$ can also be used to distinguish AD from controls and FTD, DLB, VD and major depression.[34] Furthermore, the concentration of p-tau$_{231}$ has shown longitudinal decline from mild to moderate AD.[30]

1.3 Novel CSF Biomarkers

Recently, 2 novel CSF biomarkers in AD have been proposed; visinin-like protein-1 (VILIP-1),[35] and chitinase-3-like protein-1 (YKL-40).[36] VILIP-1 is a neuron-specific intracellular calcium sensor protein.[37] An increase in CSF VILIP-1 has been observed in AD, and VILIP-1 is negatively correlated with Mini-Mental state examination.[35] VILIP-1 is a strong predictor of future cognitive decline in individuals with MCI/mild dementia and in cognitively normal control subjects.[35]

YKL-40, which is another candidate of biomarkers in CSF, is an astrocytic protein that is up regulated in neuroinflammatory conditions.[38] In two reports, YKL-40 performed nearly as well as the core biomarkers for both diagnosis and prognosis in AD versus control subjects.[36] However these results were not replicated in a subsequent study.[11]

2. Blood (plasma and serum)[5,6]

As mentioned previously, there are several drawbacks of CSF biomarkers such as an invasive CSF collection by LP and potential side effects, such as intracranial hypotension.[5] In addition, patient screening and patient follow-up analysis over several years is difficult and often problematic.[5] Therefore, there is much need for further research into the

biomarkers of other body fluids in the diagnosis AD.[11] Plasma/serum analysis is the gold standard in clinics, because they are minimally invasive, as compared with CSF, and therefore easily screened, collected, processed and followed up over several years.[5,11]

Because of the complex and time-consuming processing of blood cells,[5] identification of reliable biomarkers for AD in peripheral blood (plasma and serum) has been disappointing.[6,11] It is still unknown how much the concentration of blood directly correlates with pathological changes of the brain in AD, and it is difficult to prove changes in the levels of blood biomarkers in each of study.[11] Another limitation of plasma data is that changes are minimal and heterogeneous.[5] Plasma changes reflect a broad spectrum, not all necessarily related to AD.[5]

2.1 Plasma Aβ42

There are various inconsistent findings from the many published studies of plasma Aβ species.[39] Most studies find no change of plasma Aβ species, whereas some groups report slightly higher plasma levels of either $A\beta_{42}$ or $A\beta_{40}$ in AD, despite broad overlap between AD and control groups.[6] Plasma Aβ are particularly increased in familial AD and Down syndrome, but results are inconsistent with sporadic AD.[34] Some studies report that a high level of plasma $A\beta_{42}$, or a high $A\beta_{42}/A\beta_{40}$ ratio, is an indicator of increased risk for future AD, however, other studies have reported the contrary.[6]

2.2 Plasma Tau

A report showed that plasma tau decreases in AD,[40] whereas another study found tau increases in AD.[41] These differences probably result from the variability created by extremely low levels of tau in plasma.[6]

2.3 Novel Blood Biomarkers

Novel serum candidates include C-reactive protein (CRP)[42] and the presence of antibodies in serum that recognize selective peptid ligands in AD versus control samples.[43] More work needs to be done before blood biomarkers can be considered useful for AD diagnosis and prognosis.[6]

Imaging biomarkers

The dynamic model of the AD pathological cascade showed temporal ordering of biomarker abnormalities.[44] In the analysis of CSF biomarkers and structural MRI in participants with cognitive normal, MCI or AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI), CSF $A\beta_{42}$ was abnormal more often than t-tau or hippocampal volume, and CSF t-tau was abnormal more often than hippocampal volume only in cognitively normal people.[18] These results from the ADNI mean that amyloid deposition is an early event and that hypometabolism or hippocampal atrophy precedes.[45]

A longitudinal study of FDG PET and amyloid PET in mild AD noted little change in the anatomical extent of amyloid PET over time, whereas FDG PET hypometabolism expanded significantly.[46] In other words, by the time patients became demented, amyloid deposition was static whereas the expansion of FDG hypometabolism was continuing.[46] These results suggested that amyloid deposition has an early and subclinical impact on cognition that precedes metabolic changes, and hypometabolism becomes more pronounced later in the course of the disease.[47]

1. MRI Biomarkers

Volumetric MRI is one of the most studied imaging biomarkers. A marked decrease in normalized whole brain volume and in the hippocampus and entorhinal cortex volume is observed in AD.[48] Volumetric MRI is able to be performed as good biomarkers for diagnosis and prognosis, however, it is especially useful in the more advanced clinical stages of AD compared to CSF biomarkers.[49]

Both task-based and resting-state functional MRI (fMRI) detect changes in connectivity between areas of the brain while an individual is performing a task or resting.[6] fMRI showed differences between individuals with MCI versus control subjects on task based assessments.[50] In AD, default mode network resting connectivity is weakened, whereas in some cases, other networks have increased

activity.[51]

Arterial spin labeling (ASL) MRI is an emerging biomarker for measuring functional change associated with neurodegenerative conditions.[52] Results using ASL MRI in patients with clinical AD showed hypoperfusion to posterior cingulate, precunes, inferior parietal, and lateral prefrontal cortices.[53] ASL can also distinguish AD from FTD, and dissociated areas of hypoperfusion in AD and FTD are consistent with areas of significant histopathologic burden in these neurodegenerative diseases.[53] Changes in cerebral blood flow (CBF) measured by ASL MRI appear to overlap considerably with alterations of brain metabolism measured by FDG PET.[54]

2. PET Biomarkers

FDG-PET is a highly studied radioligand that acts as an indicator of glucose metabolism and neuronal activity.[6] Reductions in FDG-PET are observed in AD in the posterior cingulate and medial temporal lobe early in the disease process and gradually expand to areas including the frontal association cortices, providing both diagnostic and prognostic capabilities.[55] However, because these changes are not seen until the symptomatic phase of AD,[44] amyloid PET with development of the first radioligand specific to fibrillar Aβ, Pittsburgh Compound B (PiB), has been used as biomarkers.[56] In AD, levels of fibrillar Aβ are significantly increased when measured by amyloid PET,[57] this finding inversely correlates with CSF $A\beta_{42}$ levels and offer some value for diagnosis and prognosis in early stages of the disease, including the preclinical period.[58] Other amyloid imaging radioligands such as florbetapir, flutemetamol, florbetaben, and AZD4694 are also developed.[59] Florbetapir (also known as Amyvid) was recently approved by the Food and Drug Administration for use in patients being evaluated for AD and other causes of cognitive decline.[60]

Conclusion

There is no doubt that CSF and imaging biomarkers play a vital role in the early diagnosis of preclinical AD. In addition, novel biomarkers should be validated across large cohorts to diagnose preclinical and symptomatic AD and to exclude other dementias.

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