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Biochemical Markers and Genetic Risk Factors in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia, affecting over 35 million people worldwide. With increasing life expectancy and aging populations, the prevalence of AD is projected to rise dramatically in the coming decades. There is an urgent need for early diagnosis and effective treatments to slow disease progression. Biochemical markers that reflect underlying disease pathology and predict future cognitive decline offer great promise in improving early detection and monitoring treatment efficacy. This review summarizes the current literature on established and emerging biochemical markers associated with AD pathology, including beta-amyloid, tau proteins, inflammatory cytokines, oxidative stress markers, homocysteine, and cholesterol metabolites. It examines their potential roles as diagnostic and prognostic indicators of AD. The review also discusses risk factors like elevated plasma cytokines, homocysteine, and cholesterol that may identify individuals at higher risk for subsequent cognitive decline. Combining fluid biomarkers and neuroimaging improves diagnostic accuracy and will likely play a key role in early identification of AD in the future. More longitudinal studies are needed to validate the clinical utility of biomarker panels for early detection and tracking disease progression.

Introduction

Alzheimer's disease (AD) is characterized by progressive impairment in memory, language, visuospatial skills, and executive functions. It is the most common cause of dementia, accounting for 60-80% of cases (Alzheimer's Association, 2022). The hallmark pathologies are extracellular amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles containing hyperphosphorylated tau protein. These pathologies are thought to accumulate years before symptom onset, initially in medial temporal lobe structures critical for memory. Synaptic and neuronal loss eventually leads to cortical atrophy and cognitive decline.

AD is a major public health issue that affects over 35 million individuals globally, with prevalence projected to triple by 2050 as populations age (Prince et al., 2016). There are currently no disease-modifying treatments, and approved medications provide only modest symptomatic relief without altering the course of decline. This highlights the critical need for early diagnosis prior to extensive neuronal damage, when interventions are likely to be more effective.

Biochemical markers in cerebrospinal fluid (CSF) and blood that reflect underlying AD pathology have potential to improve early detection, differential diagnosis, prognosis, and tracking treatment response. This review summarizes the literature on established and emerging fluid biomarkers associated with key pathogenic processes in AD, including beta-amyloid accumulation, tau-mediated neuronal injury, neuroinflammation, oxidative stress, vascular factors, and cholesterol dysregulation. It examines their roles as diagnostic, prognostic, and theranostic indicators of AD progression.

Beta-amyloid

Amyloid precursor protein (APP) is cleaved by beta and gamma secretases to generate abeta (Aβ) peptides of varying lengths. Aβ42 is prone to aggregate into soluble oligomers and insoluble fibrils that accumulate as plaques. Reduced CSF Aβ42, reflecting sequestration in plaques, is a well-established biomarker for AD (Blennow et al., 2015). Numerous studies indicate CSF Aβ42 has over 80% sensitivity and specificity in distinguishing AD patients from normal controls and non-AD dementias like frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB) (Hansson et al., 2006; Lewczuk et al., 2004). CSF Aβ42 is also reduced in mild cognitive impairment (MCI) patients who progress to AD dementia compared to stable MCI cases, suggesting utility for predicting conversion risk (Hansson et al., 2006; Lewczuk et al., 2004).

Longitudinal studies demonstrate CSF Aβ42 declines over time in AD but remains stable in normal aging (Toledo et al., 2013). The Aβ42/Aβ40 ratio improves diagnostic accuracy over Aβ42 alone by accounting for inter-individual variations in total Aβ production (Hansson et al., 2007; Lewczuk et al., 2009). Plasma Aβ assays are being developed but require standardization, with conflicting results reported thus far (O'Bryant et al., 2015; Vergallo et al.,

2019). Overall, CSF Aβ42 is a reasonably specific early marker of brain amyloidosis that can identify individuals likely to progress from MCI to AD dementia.

Tau Proteins

Tau proteins promote microtubule assembly and stability in neurons. Hyperphosphorylation due to Aβ oligomers causes tau dissociation and aggregation into neurofibrillary tangles, disrupting axonal transport. CSF total tau (T-tau) and phosphorylated tau (P-tau) reflect neurodegeneration and tangle pathology in AD (Blennow et al., 2015). Numerous studies report elevated T-tau and P-tau levels in AD compared to controls, with moderate sensitivity around 80% but lower specificity of 60-75% due to overlap with other dementias (Hampel et al., 2010). T-tau is less specific than P-tau, which distinguishes AD from non-AD dementias like DLB, FTD, and vascular dementia more accurately (Hampel et al., 2004).

Both T-tau and P-tau are increased in MCI patients who progress to AD compared to stable MCI, serving as early markers of neurodegeneration prior to symptom onset (Buchhave et al., 2012; Hampel et al., 2004). Elevated tau precedes Aβ changes, suggesting tau abnormalities are an earlier event (Fagan et al., 2007). Longitudinally, tau progressively rises as cognition declines in AD patients (Samgard et al., 2010). Plasma assays are in development but less reliable than CSF thus far (Mattsson et al., 2016). In summary, CSF tau biomarkers reflect disease intensity and progression, help predict conversion risk in MCI, and aid differential diagnosis.

Neuroinflammation

Glial activation and inflammatory cytokines are upregulated in AD brains, possibly induced by Aβ plaques. Candidate plasma and CSF inflammatory biomarkers include C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor alpha (TNF-α) (Heneka et al., 2015). However, several meta-analyses report inconsistent results, with insufficient evidence that peripheral inflammatory markers differ significantly between AD patients and controls (Lui et al., 2016; Peng et al., 2005; Song et al., 2009). CSF studies also found no consistent differences except for trends toward elevated IL-6 and IL-1β in AD (Jia et al., 2016; Pereira et al., 2014).

While levels do not clearly distinguish AD cases from controls, higher peripheral inflammatory markers correlate with poorer cognitive scores at baseline and subsequent decline in initially normal elders, suggesting potential value as prognostic risk indicators (Guerreiro et al., 2007; Weaver et al., 2002). Anti-inflammatory treatments like NSAIDs may lower AD risk, implying inflammation contributes to pathogenesis early in the disease process (Heneka et al., 2015). Overall, current data does not support inflammatory biomarkers for diagnosis, but they may help identify individuals vulnerable to future cognitive impairment. Further prospective studies are needed.

Oxidative Stress

Oxidative damage from reactive oxygen species contributes to neuronal injury in AD. Isoprostanes, a prostaglandin byproduct of lipid peroxidation, provide an in vivo measure of oxidative stress. Several groups found elevated F2-isoprostanes, especially those derived from docosahexaenoic acid (neuroprostanes), in AD brains and CSF compared to controls (Montine et al., 2005; Pratico et al., 2000; Yao et al., 2003). Fewer studies examined plasma and urine isoprostanes in AD, with inconsistent results possibly due to comorbidities like smoking and vascular disease that confound measurements (Montine et al., 2002; Praticò et al., 2002). Overall, CSF neuroprostanes show promise as specific indicators of CNS oxidative injury in AD but require further verification. Other oxidative biomarkers like 8-hydroxyguanosine and 3-nitrotyrosine are increased in AD CSF but lack sufficient validation thus far (Abe et al., 2002; Tohgi et al., 1999).

Peripheral markers of antioxidant activity, including vitamin E, vitamin C, carotenoids, and antioxidant enzymes like superoxide dismutase (SOD), show no consistent differences between AD and controls (Jimenez-Jimenez et al., 1997; Rinaldi et al., 2003). However, higher vitamin E and SOD levels in elders correlate with subsequent cognitive decline, suggesting possible value as prognostic risk markers (Berr et al., 2000; Schmidt et al., 1998). In summary, CSF isoprostanes are promising specific markers of neurodegeneration that deserve further research, while circulating antioxidant levels may help predict risk of future impairment.

Homocysteine and B vitamins

Homocysteine is a sulfur amino acid derivative that accumulates in folate and vitamin B12 deficiency states. Elevated plasma homocysteine is an independent risk factor for cardiovascular disease and stroke (Wald et al., 2002). Cross-sectional studies show higher homocysteine in AD patients versus controls, with levels correlating inversely with cognitive scores (Clarke et al., 1998; Seshadri et al., 2002). The risk relationship persists after adjusting for confounds like renal function, nutrition, and APOE genotype. Longitudinal studies report baseline homocysteine levels predict cognitive decline and AD development in a dose-response fashion (Seshadri et al., 2002; Teunissen et al., 2003).

Related B vitamins folate, B12, and B6 are cofactors in homocysteine metabolism. Low levels correlate with cognitive impairment and predict future decline (Ramos et al., 2005; Wang et al., 2001). Homocysteine correlates negatively with folate and B12, implying these nutrients influence AD risk through effects on homocysteine (Clarke et al., 1998). Overall, homocysteine and B vitamins appear useful as prognostic markers, although routine

screening is not currently recommended (Clarke et al., 1998; Wald et al., 2002). B vitamin supplementation lowers homocysteine but thus far shows no clear benefit on cognition in randomized trials (Malouf & Grimley Evans, 2008). Further research is needed on utility of these biomarkers in AD.

Cholesterol and 24S-hydroxycholesterol

Cell culture, animal model, and genetic studies link altered cholesterol metabolism to AD pathogenesis. Cholesterol promotes Aβ production and is found in senile plaques (Pani et al., 2009; Puglielli et al., 2003). Epidemiologic studies report midlife elevations in serum cholesterol associate with higher subsequent AD risk, while late-life levels decline shortly before symptom onset (Kivipelto et al., 2002; Mielke et al., 2005; Tan et al., 2003). Statins that reduce cholesterol appear protective against AD, supporting a role of dyslipidemia in AD development (Jick et al., 2000; Wolozin et al., 2000).

Brain cholesterol metabolism yields 24S-hydroxycholesterol (24OHC) as a primary metabolite. This crosses into blood and CSF, offering a relatively specific indicator of CNS cholesterol turnover. Most studies report elevated 24OHC in AD and MCI CSF versus controls, reflecting increased turnover during neurodegeneration (Herrmann et al., 2002; Papassotiropoulos et al., 2002; Schönknecht et al., 2002). Findings in plasma are mixed, with mild elevations in early disease stages declining later as brain tissue shrinks (Herrmann et al., 2002; Hyyppä et al., 2003; Lütjohann et al., 2000). Additional research on 24OHC in CSF and plasma is needed to clarify its relationship with AD progression.

Multimodal Biomarkers

Given the heterogeneous pathology, panels combining biomarkers related to Aβ plaques, tau tangles, neurodegeneration, and vascular factors will likely prove optimal for early detection. For example, the ratio of CSF T-tau to Aβ42 accurately distinguishes AD dementia and MCI cases from normal controls, performs better than either marker alone, and predicts progression from MCI to AD (de Souza et al., 2011; Hansson et al., 2006; Shaw et al., 2009). Adding hippocampal volume from MRI to CSF markers further improves diagnostic accuracy and prognostics over single modalities (Chen et al., 2011; Ewers et al., 2012; Vos et al., 2013). Ongoing research aims to validate multifactorial algorithms incorporating imaging, cognition, genetics, plasma markers, and demographics with CSF biomarkers to improve diagnostic precision and better predict individual risk (Jack et al., 2010).

Conclusions

In summary, considerable data supports roles for CSF Aβ42, tau, and neuroimaging as useful diagnostic and prognostic markers for AD. Work is ongoing to validate plasma assays and combinatorial multimodal approaches. While promising, most biomarkers require further verification in diverse clinical settings before widespread adoption for routine diagnostic screening. Combinations with clinical assessment will likely yield the most accurate early diagnoses. Longitudinal studies are needed to assess utility for predicting outcomes and monitoring treatment response in pre-symptomatic and early stage AD patients. This remains a very active area of research that will continue advancing our ability to detect and treat AD early in its course.

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