Cerebrospinal Fluid Biomarkers of Alzheimer Disease

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Abstract

Alzheimer disease (AD) is a chronic neurodegenerative disorder and the most common cause of dementia in the elderly. Current international guidelines for the clinical diagnosis of AD consider the diagnosis to be both clinical and biological. It requires a specific clinical phenotype and a confirmed biological origin based on biomarkers of amyloid and tau pathology. In Russia, only a few research centers perform laboratory diagnosis of AD using cerebrospinal fluid (CSF) biomarkers. Better access to laboratory diagnosis of AD and wider use of CSF biomarkers in clinical practice will help to assess the true prevalence of AD in the Russian population and to select patients for targeted pathogenic therapies based on the use of monoclonal antibodies against abnormal brain proteins, which have been actively developed in recent years. This review summarizes information on the main CSF biomarkers of AD and their diagnostic and prognostic value.

Keywords: *Alzheimer's disease; dementia; biomarkers for Alzheimer disease; cerebrospinal fluid biomarkers*

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Диагностические ликворные биомаркеры при болезни Альцгеймера

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Аннотация

Болезнь Альцгеймера (БА) – хроническое нейродегенеративное заболевание и самая распространённая причина деменции в пожилом возрасте. Согласно последним международным рекомендациям по клинической диагностике БА, данный диагноз является клинико-биологическим: он требует наличия специфического клинического фенотипа и подтверждения биологической природы заболевания на основании исследования биомаркеров амилоидной и тау-патологии. В России методы лабораторной диагностики БА с исследованием ликворных биомаркеров проводятся лишь в отдельных научно-исследовательских центрах. Расширение доступности лабораторной диагностики БА и более широкое использование ликворных биомаркеров в клинической практике позволит оценить реальную распространённость БА в российской популяции, а также в ближайшем будущем отбирать пациентов для активно разрабатываемой в последние годы таргетной патогенетической терапии заболевания, основанной на применении моноклональных антител против патологических церебральных белков. В данном обзоре обобщена информация об основных биомаркерах БА в цереброспинальной жидкости и их диагностической и прогностической значимости.

Ключевые слова: *болезнь Альцгеймера; деменция; биомаркеры болезни Альцгеймера; ликворные биомаркеры*

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Introduction

Alzheimer disease (AD) is a chronic neurodegenerative disorder and the most common cause of dementia in the elderly [1]. Neuropathologically, AD is characterized by the deposition of beta-amyloid (Aβ) in the brain as extracellular plaques and the formation of intracellular neurofibrillary tangles of phosphorylated tau protein [2].

In Russia, there are approximately 9,000 registered patients with AD [3]. However, it is estimated that more than 90% of AD cases in Russia remain undiagnosed [4]. This is mainly due to a lack of awareness among primary care physicians about the early signs of AD (when symptoms are interpreted as part of normal aging or cerebrovascular disease), a reluctance to make the diagnosis at more advanced stages because of the potential social consequences, or the presence of an atypical clinical phenotype that makes it difficult to identify the nature of the neurodegenerative process without additional diagnostic tools.

Until recently, the diagnosis of AD was based primarily on clinical data, namely on the development of a typical cognitive deficit [5]. However, according to the latest guidelines from the International Working Group for the Clinical Diagnosis of Alzheimer Disease (2021), diagnosis of AD should be based on both clinical and biological features and requires a specific clinical phenotype and confirmation of biological origin based on amyloid and tau pathology biomarkers [6]. Amyloid pathology can be confirmed by low levels of $A\beta_{1-42}$ in the cerebrospinal fluid (CSF) or the detection of abnormal amyloid deposition in the brain using positron emission tomography (PET). Tau pathology can be diagnosed by high CSF levels of phosphorylated tau protein or abnormal deposition of tau protein identified by brain PET with an appropriate ligand.

In Russia, only a few research centers are able to perform laboratory diagnosis of AD based on CSF biomarkers, whereas it remains inaccessible for most Russian clinics [7–10]. PET scans with ligands for Aβ and tau proteins are not available in every clinic in Russia. However, the need to verify the diagnosis for targeted therapy will soon require a sharp increase in the availability of laboratory diagnostic tools for AD as well as a wider clinical use of CSF biomarkers (as a more accessible method compared to PET).

The **aim** of this review was to summarize data on the key CSF biomarkers of AD and their diagnostic and predictive value.

Main Pathogenic Mechanisms of Alzheimer Disease

In 1906, Alois Alzheimer first described a clinical case of dementia in a young woman with progressive memory loss, speech, movement and behavioral disorders, and hallucinations. Postmortem brain pathomorphology revealed macroscopic signs of extensive brain atrophy. Using a novel silver impregnation technique for brain histology, Alzheimer identified typical neuropathologic changes namely extracellular amyloid plaques and intracellular neurofibrillary tangles [11]. n 1987, the gene *APP* (amyloid precursor protein), which encodes the amyloid precursor protein located on chromosome 21, was identified [12]. In 1992, the official amyloid hypothesis of AD was proposed [13].

APP is a transmembrane protein found in many tissues of the body. However, its physiological functions are not fully understood. This protein may be involved in learning, memory and neuroplasticity, including synaptogenesis, which may be a key element of neuroprotection [14]. Proteolytic cleavage of APP can involve two pathways: a non-amyloidogenic pathway that results in the production of soluble α-amyloid and an amyloidogenic pathway that results in the formation of insoluble and aggregation-prone Aβ fragments [15]. According to the amyloid theory, a critical role in AD is attributed to the altered cleavage pattern of the APP protein, leading to excessive production of Aβ peptides. Aβ is formed by the sequential cleavage of APP by specific enzymes such as β-secretase and γ-secretase (identified as a presenilin complex) [16]. γ-Secretase-mediated APP cleavage results in the production of amyloid peptides consisting of 36–43 amino acids [17]: a peptide consisting of 40 amino acids ($A\beta_{40}$) is produced in larger quantities and a peptide consisting of 42 amino acids ($A\beta_{42}$) is produced in smaller quantities [18]. Although different isoforms of Aβ can be detected in AD patients, the levels of $A\beta_{42}$ and $A\beta_{40}$ and their ratio are considered the most reliable biomarkers for AD [19].

Historically, hyperproduction of Aβ was thought to be the main cause of AD [20, 21]. In recent years, however, a defect in Aβ clearance mechanisms has been suggested to play a major role [22, 23]. Yoon *et al.* identified four main mechanisms of Aβ clearance, divided into non-enzymatic and enzymatic pathways [24]. The non-enzymatic pathway includes three mechanisms:

1) Drainage of interstitial fluid into the blood through periarterial Virchow–Robin spaces [22];
2) Phagocytosis by microglia or astrocytes [25];
3) Transport across blood vessel walls, mediated by some clearance receptors (low density lipoprotein receptor-related protein 1 (LRP1); very-low-density-low-density lipoprotein receptor (VLDLR); P-glycoprotein) [26].

The enzymatic pathway involves the cleavage of Aβ by proteases, including neprilysin [27], insulin-degrading

enzyme [28], matrix metalloproteinase-9 [29], and glutamyl carboxypeptidase II [30]. The imbalance between Aβ peptide production and clearance initiates a cascade of pathological reactions that are the main cause of AD development [15].

Intracellular accumulation of soluble amyloidogenic Aβ oligomers has a neurotoxic effect even before the formation of extracellular plaques, leading to synaptic dysfunction, postsynaptic hyperexcitability, disruption of homeostasis, and increased production of reactive oxygen species in neuronal mitochondria [31, 32]. The extracellular aggregates of insoluble fibrils containing Aβ peptides (amyloid plaques) also have a neurotoxic effect. Simultaneous dysfunction of astrocytes and microglia, the brain's immune cells, develops. Overproduction of inflammatory cytokines occurs and phagocytosis of Aβ is impaired. These processes activate cell signaling pathways associated with apoptosis and neuronal death [33].

Tau protein is associated with microtubules, is expressed primarily in neurons and is encoded by the *MAPT* (microtubule-associated protein tau) gene located on chromosome 17. Neuroimaging studies show that the onset and location of tau pathology correspond to both the onset and type of cognitive deficit [34, 35]. The main functions of this protein include stimulation of tubulin polymerization, stabilization of microtubules, and transport of intracellular organelles [36]. Tau aggregation is a multi-step process that likely begins with the hyperphosphorylation of tau protein and its detachment from microtubules. During aggregation, tau protein moves into the somatodendritic regions of neurons where further phosphorylation and structural changes occur. Misfolded proteins begin to aggregate, forming freely spreading pathogenic oligomers, which leads to further disease development, affecting healthy cells and causing neuronal death [37].

Several mechanisms leading to tau hyperphosphorylation and conformational changes and formation of neurofibrillary tangles are described:
1) activation by Aβ proteins of specific enzymes that catalyze hyperphosphorylation;
2) neuroinflammation triggered by Aβ deposition and promoting the activation of pro-inflammatory cytokines;
3) decreased ability to degrade hyperphosphorylated tau proteins;
4) axonal transport defect [38].

Aβ oligomers first induce phosphorylation of tau protein at specific epitopes and then cause cytoskeleton collapse and neuronal degeneration [39].

Cerebrospinal Fluid Biomarkers of Alzheimer Disease

Lumbar puncture is a routine medical procedure used for diagnostic and therapeutic purposes. The CSF is in direct contact with the extracellular space of the brain and spinal cord, and its biochemical changes may reflect the characteristics of neurodegenerative diseases. CSF is the main biological fluid used for the diagnosis of AD [40]. $Aβ_{1-42}$ and $Aβ_{1-40}$, total tau (t-tau), and phosphorylated tau (p-tau) are the best-known CSF biomarkers for AD [41].

$Aβ_{1-42}$

The $Aβ_{1-42}$ protein in CSF is recognized as a key biomarker for AD. Reduced levels of $Aβ_{1-42}$ have been shown in several international studies to be highly accurate in diagnosing dementia and mild cognitive impairment in AD. This biomarker has high sensitivity and specificity in diagnosing AD at all stages [42–45]. Reduced levels of $Aβ_{1-42}$ in CSF are found to be the earliest pathological change in AD, preceding Aβ ligand PET imaging [46]. The concentration of $Aβ_{1-42}$ declines long before the onset of clinical symptoms [47], making this biomarker particularly suitable for early diagnosis [48].

The mechanisms leading to decreased CSF levels of $Aβ_{1-42}$ in patients with AD are still unclear. Some authors suggest that this may be due to excessive deposition of $Aβ_{42}$ in amyloid plaques, as the aggregated state impedes transport of $Aβ_{1-42}$ from the interstitial fluid into the CSF [49]. Other hypotheses include decreased production rates of $Aβ_{42}$ [23], increased $Aβ_{42}$ degradation due to proteolytic breakdown [50] or microglial phagocytosis [51], as well as increased clearance of $Aβ_{1-42}$ into the blood [52], although these are considered less likely [53].

One limitation of isolated $Aβ_{1-42}$ studies in CSF is the frequent finding of decreased levels of this biomarker in other neurodegenerative diseases, such as cerebral microangiopathy [54], dementia with Lewy bodies [55], Creutzfeldt–Jakob disease [56], and frontotemporal dementia (FTD) [57]. Although the levels of $Aβ_{1-42}$ in AD are usually significantly lower than in these diseases, this overlap limits the differential diagnosis.

Aβ1-40

While $Aβ_{1-42}$ constitutes approximately 10% of the total Aβ peptide population, the protein $Aβ_{1-40}$ is the dominant form in the brain, CSF, and plasma [58]. The total concentration of Aβ varies little between diseases, and the concentration of $Aβ_{1-40}$ does not differ significantly between patients with AD, healthy individuals, and patients with dementia of other origin [59]. Therefore, CSF levels of $Aβ_{1-40}$ may be considered the most accurate reflection of total brain Aβ burden, although the value of this test in isolation remains controversial. $Aβ_{1-40}$ levels are primarily used to evaluate the $Aβ_{1-42}/Aβ_{1-40}$ ratio.

The $Aβ_{1-42}/Aβ_{1-40}$ Ratio

The $Aβ_{1-42}/Aβ_{1-40}$ ratio was proposed in the late 1990s to improve the differential diagnosis of AD [60]. This ratio is important and accounts for constitutive interindividual differences in total CSF burden of Aβ between high and low amyloid production [61]. Studies have found a high correlation between a lower $Aβ_{1-42}/Aβ_{1-40}$ ratio and higher levels of total and phosphorylated tau protein [62]. Patients with a lower $Aβ1_{-42}/Aβ_{1-40}$ ratio show a faster cognitive and functional decline and a more rapid decline in episodic memory [63]. These data demonstrate the advantage of using the $Aβ_{1-42}/Aβ_{1-40}$ ratio over isolated CSF levels of $Aβ_{1-42}$ for predicting the progression of cognitive impairment.

Total Tau Protein

The first study that successfully evaluated total t-tau in CSF was published in 1995 and showed that t-tau levels were significantly higher in patients with AD compared to patients with other neurodegenerative diseases and controls [64]. Similar results have been found in hundreds of other studies [65]. However, elevated CSF levels of t-tau were later found in some acute conditions (such as stroke [66], traumatic brain injury [67], Wernicke encephalopathy [68]), as well as in rapidly progressive neurodegenerative diseases (such as Creutzfeldt–Jakob disease [69]). Based on the data obtained, the level of t-tau is proposed to be used as a marker of the activity of the neurodegenerative process or the severity of acute neuronal damage in the brain [70]. In patients with AD, higher levels of t-tau may predict faster clinical progression of the disease [71].

Phosphorylated Tau Protein

Tau protein undergoes multiple post-translational modifications, such as glycosylation [72], glycation (non-enzymatic glycosylation) [73], phosphorylation, etc. Phosphorylation is the most important modification and level phosphorylation regulates the biological activity of the tau protein [74]. Normally, more than 30 different sites of the protein at serine, threonine, or proline positions are phosphorylated [75]. These modifications can control normal biological functions of tau, such as regulating the stability of microtubules, and lead to the development of pathological processes associated with the protein's ability to self-assemble into neuronal filaments found in neurodegenerative diseases [76].

Tau protein phosphorylated at threonine 181 (p-tau181) in CSF is the best understood form of p-tau as an AD biomarker used in current disease diagnosis [77]. This biomarker (in combination with $A\beta_{42}$) accurately discriminates between patients with AD and healthy individuals and can also predict cognitive decline in preclinical and prodromal stages of the disease [78]. Levels of p-tau181 are significantly higher in AD than in other tauopathies, including FTD, progressive supranuclear palsy, and corticobasal degeneration. Therefore, this parameter can be used in the differential diagnosis of dementia in these conditions [57, 79, 80].

The levels of tau phosphorylated at positions 217 (p-tau217) and 231 (p-tau231) have received considerable attention in recent years. For example, elevated levels of p-tau217 in CSF have been shown to be the most specific parameter for detecting both preclinical and advanced stages of AD [81]. CSF p-tau217 levels in patients with prodromal stage and AD dementia were several times higher than p-tau181 levels in the same patients [82]. The superiority of p-tau217 over p-tau181 has also been demonstrated in studies showing stronger correlations of p-tau217 with amyloid PET results [83].

For p-tau231, there is evidence that it is most sensitive to the earliest manifestations of amyloid pathology in the medial orbitofrontal cortex, precuneus, and posterior cingulate cortex, before the threshold of pathological amyloid ligand accumulation is reached on PET scans [84]. This biomarker is thought to reach diagnostically significant abnormal levels only at disease onset [85] and may be key to identifying the recently described pre-amyloid phase of AD [86], which occurs before the abnormal accumulation of Aβ is detectable by PET. Stronger correlations between CSF p-tau231 levels and amyloid PET burden in individuals without clinically evident cognitive impairment suggest that increases in CSF p-tau231 levels occur during the lag phase of Aβ protein aggregation in the brain [84].

Markers of Neurodegeneration and Microglial Activation

Although a hallmark of AD is the formation of Aβ and tau protein aggregates in the brain, there are also typical neuroinflammatory responses that occur in the affected brain areas, leading to neuronal dysfunction, neuronal death, and synapse loss [87]. Further research into the diverse pathogenetic mechanisms of AD is needed to identify alternative therapeutic approaches.

Accumulating data in recent years suggest an association between synaptic loss in AD and neurogranin (Ng). Neurogranin is a neuron-specific postsynaptic protein that is abundantly expressed in the brain, particularly in the dendrites of hippocampal and cortical neurons [88]. It binds to calmodulin at low calcium ion concentrations and regulates synaptic plasticity of neurons by modulating Ca^{2+}/calmodulin-dependent pathways. It is also involved in long-term potentiation, which is important for learning and memory processes [89]. Another hallmark of AD is an increase in CSF levels of Ng, which gradually increases with cognitive decline and negatively correlates with Mini Mental State Examination scores, likely reflecting synaptic damage due to Aβ aggregation with plaque accumulation [90, 91]. Some authors report a significant increase in CSF Ng levels in AD compared to Lewy body dementia, FTD, and amyotrophic lateral sclerosis [92], while others report only a high correlation between CSF Ng levels and CSF t-tau and p-tau181 levels [93]. Therefore, the value of CSF Ng level assessment is still controversial.

Neurofilament light chain (NfL) is a scaffold protein of the neuronal cytoskeleton that plays an important role in axon and dendrite branching and growth. Following axonal injury, CSF NfL levels increase and serve as a biomarker for axonal injury and neurodegeneration [94]. In recent years, the use of this biomarker to assess the progression of various neurological diseases, including AD, has increased significantly [95]. Higher CSF levels of NfL are also found in cognitively healthy individuals with hippocampal atrophy on neuroimaging [96] and in preclinical stages of AD [97, 98]. Longitudinal studies in patients with AD have shown that an increase in CSF NfL level is associated with a more intense progression of brain atrophy and cognitive decline. Therefore, higher NfL levels in early clinical stages of AD appear to predict faster conversion to dementia [99]. However, the specificity of this biomarker for AD is low since the highest levels are found in other neurodegenerative disorders such as amyotrophic lateral sclerosis, FTD, corticobasal degeneration, and progressive supranuclear palsy [100].

The pathogenesis of AD is also accompanied by reactive astrogliosis, which is characterized by morphological, molecular, and functional remodeling of astrocytes [101]. Glial fibrillary acidic protein (GFAP) is a type III intermediate filament protein that is predominantly expressed by astrocytes in the CNS [102]. In animal models, high levels of GFAP expression are found in astrocytes of the hippocampus, the corpus callosum and the cerebral peduncles [103]. Its expression is significantly increased in neurodegenerative diseases, including AD, reflecting neuroinflammatory processes and astrocyte activation [104]. In AD, elevated CSF levels of GFAP are a potential marker of progressive cognitive impairment; these levels have been shown to increase as cognitive deficits progress [105]. However, these changes are not specific to AD, because an increase in GFAP levels with progressive cognitive impairment has also been described in patients with Parkinson's disease, FTD, multiple sclerosis, and other neurological disorders [106].

These biomarkers are being studied for research purposes, but are not yet used in clinical practice due to insufficient specificity for diagnosing AD.

Clinical Use of CSF Biomarkers for AD in Neurology

As mentioned above, according to the International Working Group Recommendations for the Clinical Diagnosis of Alzheimer's Disease (2021), a diagnosis of AD requires the presence of a specific clinical phenotype and confirmation of the biological origin of the disease based on biomarker testing [6]. These guidelines distinguish between common and rare AD phenotypes. The main clinical phenotypes of AD include the classic amnestic (hippocampal) variant, posterior cortical atrophy, and the logopenic variant primary progressive aphasia. Rare phenotypes include frontal (behavioral/dysregulation) variant, corticobasal syndrome, and semantic and agrammatic variants of primary progressive aphasia. It is proposed to establish probability levels for AD as the primary diagnosis based on the combination of the clinical phenotype and the results of key biomarker testing (in CSF or by PET). The diagnosis of AD is categorized as definite, probable, and possible, with additional categories of unlikely and excluded. For controversial cases, recommendations for further patient evaluation are provided (Table 1).

Conclusion

According to international guidelines, the key CSF biomarkers for the clinical diagnosis of AD (gold standard) include $A\beta_{1-42}$, $A\beta_{1-42}/A\beta_{1-40}$ ratio, and p-tau181. CSF t-tau levels can be used to assess the activity of the neurodegenerative process and predict the clinical progression of the disease. Novel biomarkers of tau pathology (including CSF p-tau217 and p-tau231 levels) could also be used to diagnose AD, because they are both highly sensitive and specific even in the preclinical stages of the disease. The clinical applicability of markers of neurodegeneration and astrocyte activation (Ng, NfL, GFAP) requires further discussion, so their use is currently warranted only in research settings.

The wider availability of CSF biomarkers in Russian clinical practice will allow for the assessment of the true prevalence of AD in the Russian population, as well as the selection of patients for targeted therapy, which has been actively developed in recent years.

Table 1. International Working Group Recommendations for the Clinical Diagnosis of Alzheimer's Disease (2021)

Phenotype	Likelihood of AD as a primary diagnosis	Further investigation
Common clinical phenotypes in AD (amnestic variant, posterior cortical atrophy, logopenic variant primary progressive aphasia)		
Amyloid positive; tau positive	Highly probable – established	None required
Amyloid positive; tau unknown	Probable	Consider a tau measure (PET, CSF)
Amyloid positive; tau negative	Probable	Consider an additional tau measure (PET, CSF)
Tau positive; amyloid unknown	Possible	Consider an amyloid measure (PET, CSF)
Tau positive; amyloid negative	Possible	Consider an additional amyloid measure (PET, CSF)
Amyloid negative; tau unknown	Unlikely	Full investigation of cause and consider a tau measure (PET, CSF)*
Amyloid unknown; tau negative	Unlikely	Full investigation of cause and consider an amyloid measure (PET, CSF)*
Amyloid unknown; tau negative	Highly unlikely – excluded	Full investigation of cause*▽
Amyloid unknown; tau unknown	Non-assessable	Consider tau and amyloid and measure (PET, CSF)
Uncommon clinical phenotypes in AD (frontal variant, corticobasal syndrome, semantic and agrammatic variants of primary progressive aphasia)		
Amyloid positive; tau positive	Probable	None required; careful follow-up needed: an incongruent clinical phenotype and neurodegeneration pattern should trigger a new investigation*
Amyloid positive; tau unknown	Possible	Consider a tau measure (PET, CSF)
Amyloid positive; tau negative	Possible	Consider an additional tau measure (PET, CSF)
Tau positive; amyloid unknown	Unlikely	Full investigation of cause and consider an amyloid measure (PET, CSF)*
Tau positive; amyloid negative	Unlikely	Full investigation of cause*
Amyloid negative; tau unknown	Highly unlikely – excluded	Full investigation of cause*▽
Amyloid negative; tau negative	Highly unlikely – excluded	Full investigation of cause*▽
Amyloid unknown; tau negative	Highly unlikely – excluded	Full investigation of cause*▽
Amyloid unknown; tau unknown	Non-assessable	Full investigation of cause and consider tau and amyloid measure (PET, CSF)*

Note. *Full investigation of cause depends on the specific clinical phenotype and can imply, for example, ^{18}F-fluorodeoxyglucose PET (FDG-PET), dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT), serum progranulin assay, genetic analysis, oculomotor recordings, or electromyoneurography. ▽Consider a new Alzheimer's disease biomarker investigation only if there is a reasonable doubt about the validity of the biomarker results.

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