Modern Approaches to the Diagnosis of Cognitive Impairment and Alzheimer's Disease: A Narrative Literature Review

Современные подходы к диагностике когнитивного снижения и болезни Альцгеймера: нарративный обзор литературы

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Review

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ABSTRACT

BACKGROUND: The aging of the world's population leads to an increase in the prevalence of age-related diseases, including cognitive impairment. At the stage of dementia, therapeutic interventions become usually ineffective. Therefore, researchers and clinical practitioners today are looking for methods that allow for early diagnosis of cognitive impairment, including techniques that are based on the use of biological markers.

AIM: The aim of this literature review is to delve into scientific papers that are centered on modern laboratory tests for Alzheimer's disease, including tests for biological markers at the early stages of cognitive impairment.

METHODS: The authors have carried out a descriptive review of scientific papers published from 2015 to 2023. Studies that are included in the PubMed and Web of Science electronic databases were analyzed. A descriptive analysis was used to summarized the gleaned information.

RESULTS: Blood and cerebrospinal fluid (CSF) biomarkers, as well as the advantages and disadvantages of their use, are reviewed. The most promising neurotrophic, neuroinflammatory, and genetic markers, including polygenic risk models, are also discussed.

CONCLUSION: The use of biomarkers in clinical practice will contribute to the early diagnosis of cognitive impairment associated with Alzheimer's disease. Genetic screening tests can improve the detection threshold of preclinical abnormalities in the absence of obvious symptoms of cognitive decline. The active use of biomarkers in clinical practice, in combination with genetic screening for the early diagnosis of cognitive impairment in Alzheimer's disease, can improve the timeliness and effectiveness of medical interventions.

АННОТАЦИЯ

ВВЕДЕНИЕ: Старение населения по всему миру ведет к увеличению распространённости ассоциированных с возрастом заболеваний, в том числе и когнитивных расстройств. На стадии деменции терапевтические вмешательства, как правило, малоэффективны. Поэтому в фокусе внимания современных исследователей и клиницистов — поиск способов ранней диагностики когнитивных расстройств, в том числе, с использованием биологических маркеров.

ЦЕЛЬ: Целью данного обзора литературы является анализ научных исследований, посвященных современному состоянию лабораторной диагностики болезни Альцгеймера, в том числе на ранних этапах развития когнитивных расстройств, с использованием биологических маркеров.

МЕТОДЫ: Авторы провели описательный обзор научных исследований, опубликованных в период с 2015 по 2023 год. Были проанализированы работы, представленные в электронных базах данных PubMed и Web of Science. Для обобщения полученной информации был использован описательный анализ.

РЕЗУЛЬТАТЫ: Рассмотрены биологические маркеры крови и ликвора, преимущества и недостатки их применения. Также описаны наиболее перспективные нейротрофические, нейровоспалительные и генетические маркеры, в том числе модели полигенного риска.

ЗАКЛЮЧЕНИЕ: Использование биомаркеров в клинической практике будет способствовать ранней диагностике когнитивных расстройств при болезни Альцгеймера. Генетический скрининг способен повысить выявляемость патологических изменений на доклиническом этапе, когда явные симптомы когнитивных нарушений еще не проявились. В совокупности активное использование биомаркеров в клинической практике в комбинации с генетическим скринингом для ранней диагностики когнитивных расстройств при болезни Альцгеймера способно повысить своевременность и эффективность медицинского вмешательства.

Keywords: *biomarkers; Alzheimer's disease; dementia; diagnosis; cognitive impairment; polygenic risk*
Ключевые слова: *биомаркеры; болезнь Альцгеймера; деменция; диагностика; когнитивные расстройства; полигенный риск*

INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia associated with progressive cognitive decline. The pathogenesis of the disease is related to molecular disruptions resulting in neuronal dysfunction and death, synaptic loss, gliosis, and neuroinflammation. AD-associated abnormalities progress quite rapidly and cause gradual maladaptation of the patient, which imposes a burden not only on the patient's immediate family, but also on the healthcare system in general. According to the World Alzheimer's Report 2015, 46.8 million people suffer from dementia worldwide. This number is expected to reach 131.5 million people by 2050 [1].

Early stages of AD may come with no obvious clinical manifestations, which makes it difficult to diagnose and undertake timely medical intervention, which is most effective at the pre-dementia stages. When making a diagnosis, a clinical practitioner evaluates the patient's history data, takes into account the family history of dementia in first-degree relatives, the physical examination and neurological examination findings, as well as the results of laboratory and imaging tests [2]. It is important to rule out endocrine and metabolic disorders, vitamin deficiencies, possible consequences of infectious diseases and cases of alcohol abuse, including psychoactive substance and drug abuse. In some cases, neuroimaging can reveal morphological changes in the central nervous system (CNS) that are not detected during clinical examination [2]; however, in the case of AD, its use is also not always informative enough due to the non-specificity of the observed structural disorders. A neuropsychological evaluation using the Mini-mental State Examination (MMSE), Montreal

Cognitive Assessment (MoCA), and space-Cog test supplements the results of the patient assessment [3].

At early stages of AD, when the clinical manifestations of the disease may not be sufficiently visible to reach a correct diagnosis, it is advisable to rely on the results of laboratory tests and genetic screening tests, in addition to clinical evaluation findings. The introduction of specific biochemical markers (biomarkers/markers) into routine clinical practice should help detect the onset of AD and trigger the required medical interventions in a timely manner. Our existing biomarker panel is very limited. In most cases, laboratory tests are limited to ruling out somatic and infectious causes of cognitive decline; in rare cases, blood or CSF tests for the β-amyloid level are performed. Therefore, the search for, study, and validation of AD biomarkers, as well as their active implementation in routine clinical practice, is a relevant issue faced not only by scientists, but also by clinical practitioners all over the world.

The aim of this literature review was to analyze scientific papers related to modern laboratory tests for AD, including tests for biomarkers at the early stages of cognitive impairment.

METHODS

The authors have carried out a descriptive review of literature published over the period from 2015 to 2023. This time period was chosen for analysis due to the growing body of research into the early diagnosis of dementia and the discovery of new promising biomarkers. Studies included in the PubMed and Web of Science electronic databases were analyzed. The search queries included the keywords “cognitive impairment”, “dementia”, “Alzheimer’s disease”, “neuroinflammation”, “biomarkers”, “neurotrophic factors”, “genetic markers”, and “polygenic risk”.

The studies were considered eligible if they included an evaluation of the use of biomarkers for the diagnosis of cognitive impairment. The review included studies related to the topic, regardless of their designs. A descriptive analysis was used to summarize the obtained information.

RESULTS

This review included the results of 60 studies related to the topic. Table S1 in the Supplementary provides the characteristics of the included scientific papers; namely, the title, authors, year, country, type of study, methods, and results.

Both blood and CSF biomarkers are used for the diagnosis of AD. The use of blood biomarkers is the most accessible and the least invasive diagnostic method. CSF markers are likely to be more specific; however, a CSF collection procedure is more invasive and not always feasible in primary care clinics. Our review discusses both well-studied biomarkers and markers the diagnostic value of which is yet to be proven. In addition to blood and CSF biomarkers, we have reviewed the use of neuroinflammatory, neurotrophic, and genetic markers of AD.

CSF biomarkers

The diagnostic criteria for AD include the assessment of three classical CSF biomarkers: total tau-protein (T-tau), phosphorylated tau-protein (P-tau), and a 42-amino acid peptide (Aβ42) that reflect the processes of neurodegeneration and the formation of neurofibrillary tangles and amyloid/senile plaques [4]. There is also a number of CSF biomarkers that seem to be promising but require further research. CSF neurogranin has been proposed as a potential neurodegeneration marker associated with AD-associated synaptic dysfunction [5] and having a prognostic value at early stages of the disease [6]. The membrane protein SNAP-25 level in CSF and the SNAP-25/Aβ42 ratio have been proposed as predictors of AD-associated cognitive decline [7]. Apolipoprotein B (apoB) can be a marker of early cognitive impairment associated with AD, particularly, the predisposition to visuospatial disorientation [8]. A recent study conducted in Canada showed that the GAP43 protein, neurogranin, SNAP25 membrane protein, and synaptotagmin 1 are potentially effective biomarkers for predicting AD development 5–7 years before the development of cognitive impairment [9]. As was demonstrated in a meta-analysis by Mavroudis et al., the level of the visinin-like protein 1 (VILIP-1) was significantly higher in AD patients compared to the control group. Compared to patients with mild cognitive impairment (MCI), the level of VILIP-1 was higher in patients with MCI progressing to AD [10].

Blood biomarkers

Blood biomarkers used for the diagnosis of AD include beta-amyloids (Aβ) and their oligomers, the tau protein, neurofibrillary tangles (NFTs), apolipoprotein E (APOE),

microRNAs, exosomes, and gut microbiota markers [11]. The following markers may be used to assess neurodegeneration: a marker for axonal damage — plasma neurofilament (NfL); a marker for glial activation — glial fibrillary acidic protein (GFAP) [12, 13]; β-synuclein [14, 15]; visinin-like protein 1 (VILIP-1) [16, 17]; and the membrane protein SNAP25 [18].

Some authors suggest assessing the levels of iron, ferritin, and cholesterol in the blood as potential markers of cognitive impairment [19]. Other researchers report the potential value of neurogranin as a marker of synaptic dysfunction, the epidermal growth factor (EGF) involved in neurogenesis in adults, as well as pancreatic polypeptide, an increased level of which may be associated with neuronal death [5].

A recent study conducted by Chinese scientists in Hong Kong resulted in the development of a diagnostic panel including 19 plasma proteins, which made it possible to separate patients with AD from the control group with an accuracy of up to 97% [20]. A team of European researchers successfully used a combination of biomarkers (Aß42/Aß40, p-tau181, ApoE4) in two independent cohorts to identify amyloid-positive patients and predict the development of AD [21]. Brazilian researchers have developed a machine learning-based diagnostic panel that includes 12 plasma proteins (ApoB, calcitonin, C-peptide, C-reactive protein, IGFBP-2, Interleukin-3, Interleukin-8, PARC, transferrin, TCP, TLS 1-309 and TN-C) and allows one to predict the slide from MCI to AD-associated dementia within the subsequent four years [22].

Mass spectrometry of a number of candidate biomarkers in serum demonstrated a statistically significant decrease in the levels of afamin, apolipoprotein E, biotinidase, and paraoxonase/arylesterase 1 in AD patients [23]. The combination of mass spectrometry with machine-learning technologies allows one to evaluate the risk of AD development in the subsequent three years in patients with MCI, using a diagnostic panel based on 31 serum biomarkers with an accuracy of ~80%, sensitivity of 79.4%, and specificity of 83.6% [23].

Neuroinflammatory markers

An increase in the concentration of pro-inflammatory markers can also serve as a prognostic risk factor of the development of dementia in AD patients [24]. However, it should be taken into account that brain inflammation can also be associated with many other disorders, including depression and multiple sclerosis [24].

Neuroinflammation leads to the formation of reactive oxygen species (ROS), chemokines, cytokines, and various secondary messengers [25]. Tissue-resident immune cells, CNS glial cells such as microglia, astrocytes, and endothelial cells are involved in the production of inflammatory mediators. Neuroinflammatory reactions lead to immune, physiological, biochemical, and psychological effects.

During the development of AD, a hyperphosphorylated tau protein forms and the accumulation of neurofibrillary tangles in the central nervous system tissues leads to the release of exosomes, which additionally enhance the expression of chemokines, such as the 3X CXCL3 chemokine ligand, and increase the level of the NLRP3 inflammasomes. Then, the synthesis of interleukin-1ß (IL-1ß) is triggered, leading to a neuroinflammatory cascade [26].

Inflammatory markers associated with neuronal damage include cytokines, the transforming growth factor-beta (TGF-β) and IL-1ß, which cause direct synaptic damage to microglia [27]. As a result, the transmission of the synaptic impulse is disrupted and the communication of the neural network deteriorates, which ultimately leads to synaptic dysfunction and neurodegenerative changes.

Based on the data collected by researcher who studied the consequences of neuroinflammation [28], a direct correlation between neuroinflammatory changes and the onset of neurodegeneration resulting in cognitive decline of varying severity may be assumed. Since mental disorders that include cognitive decline are associated with the immune response (namely, microglial activation and production of pro-inflammatory agents), tests for immunological markers may contribute to the prediction of the development of cognitive impairment [28].

According to I.K. Malashenkova et al., the following correlation between changes in the immune status and the development of cognitive impairment exists [29].

All patients with a significant deterioration of cognitive function and the development of dementia of the Alzheimer's type had systemic inflammation at the beginning of the study, which manifested itself in changes in the respective parameters. Particularly, there was an increase in the levels of the C-reactive protein and pro-inflammatory cytokines, namely IL-1β, interleukin-8 (IL-8), and the tumor necrosis factor alpha (TNFa).

Table 1. Changes in the immune status of patients with cognitive impairment [29]

Parameter Diagnosis		Mild cognitive impairment	AD severity		
			mild	moderate	severe
C-reactive protein concentration		↑	↑	↑	↑
IL-1β and TNFα cytokine concentrations		↑	↑	N	N
Humoral immunity	IgG	N	N	↓ in 50% of patients	↓↓
	IgA	N	N	N	↑
Cell-mediated immunity	NK cell count	N	↑↑	↑↑	↑↑

Note: ↑ — increase, ↓ — decrease, ↑↑ — significant increase, ↓↓ — significant decrease, N — no significant changes.

However, these markers are non-specific and a change in their concentrations may be typical for a number of disorders [29] (Table 1).

Neurotrophic markers

The neurotrophin family consists of the nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), as well as the neurotrophins NT-3, NT-4/5, and NT-6. Brain neutrophin level changes are observed in patients with various disorders, such as mental illnesses (e.g., depression and schizophrenia), parasitic diseases of the central nervous system, as well as neurodegenerative diseases such as AD [30]. In this regard, it is reasonable to assume that changes in the concentration of neurotrophins may have a diagnostic value. Do Carmo et al. investigated the NGF metabolic pathway dysregulation in connection with cholinergic dysfunction in AD patients and came to the conclusion that changes can be detected as early as at the preclinical stages of AD, which makes NGF a potentially valuable prognostic marker [31]. Scientists studying changes in the NGF metabolism in AD patients with the Down syndrome came to similar conclusions. The researchers believe that impaired metabolism of NGF may be detected as early as at the stage of MCI [32].

BDNF is a neurotrophin, and low levels of BDNF in the CNS tissues are commonly associated with neurodegenerative disorders [30]. BDNF is usually associated with neuronal survival, synapse formation, neuroplasticity, and changes in the inhibition and excitation mechanisms. The presence of a neurotoxic stimulus and concomitant neurological disorders causes a decrease in the level of BDNF, which manifests itself in cognitive impairment of varying severity [30].

In a recent study conducted in Italy, serum levels of BDNF in patients with MCI and AD were evaluated in association with BDNF gene polymorphisms (Val66Met, rs6265; C270T, rs56164415). Serum BDNF levels were significantly lower in AD patients (p=0.029), especially females (p=0.005). Serum BDNF levels were also shown to be related to the IL-1α and BDNF gene polymorphisms [33]. The researchers showed that high levels of BDNF were associated with a lower risk of neurodegenerative disorders [34]. However, the researchers evaluated the diagnostic value of BDNF differently. In a study by Qian et al., plasma levels of BDNF were decreased at the stage of MCI and increased at the stage of dementia and were dependent on a number of factors such as age, education, and occupation. Therefore, the investigators concluded that plasma levels of BDNF cannot be a reliable marker for early screening and diagnosis of AD [35].

Other neurotrophins also may have a predictive value for the diagnosis of AD. In an animal model of AD, Chinese researchers showed that the NT-3 neurotrophin improved cognitive functions by increasing neuronal differentiation [36]. The value of NT-4/5 in the early diagnosis of AD has not been sufficiently studied and requires further research. A study conducted by Mexican researchers demonstrated an inhibitory impact of NT-4/5 on the effects of BDNF [37].

Genetic markers

The existence of familial Alzheimer's disease (AD) indicates that genetic factors play an important role in the pathogenesis of this disease. The most aggressive type of AD (early-onset AD) is highly likely to be inheritable [38].

The most studied, but not the only one, genetic risk factor of AD is the presence of an ε4 allele of apolipoprotein E (APOE). The incidence of this allele among patients with AD amounts to 20–25% and is known to result in a 3-fold and a 15-fold increase in the risk of developing the disease in heterozygous and homozygous carriers,

respectively [39]. The ε2 allele of the APOE gene is associated with a low risk of AD; ε3 carriers are also significantly less likely to develop dementia compared to ε4 carriers [40]. Isoform-specific effects of apolipoprotein E in the brain affect changes in Aß, the tau protein and other neuroinflammatory, and metabolic markers. However, the exact molecular mechanisms of Aβ regulation evaluated in animal models have not been established so far. It still remains unclear whether the ε4 allele affects the AD pathogenesis by increasing the toxicity or weakening protective functions (or a combination of both). To date, no medicines to treat/prevent the progression of AD affecting the pathways of the APOE4 isoform formation have been developed. The combined therapy of increased lipidation with simultaneously decreasing lipid-free apoE4 would be an appealing approach to prevent the progression of AD. However, it is currently obvious that AD is a multifactorial disorder that is due to the changes in the expression of many various loci [40].

Genome-wide association studies (GWAS) conducted using samples from tens of thousands of AD patients and healthy donors have generated a large amount of AD-related genetic data [41, 42] and identified more than 40 loci associated with the disease [43]. Nevertheless, single nucleotide polymorphisms (SNPs) in the identified loci are likely to have little effect on the risk of developing the disease and cannot be used as independent prognostic markers [43]. This issue is typical for many multifactorial disorders. To assess the influence of genetic factors on disease development and the formation of a certain trait, a polygenic risk score (PRS) was proposed. PRS models assess the cumulative (multiplicative) influence of several SNPs, which are usually selected based on GWAS using special algorithms [44]. Each SNP is assigned an individual coefficient (which is generally a weighted odds ratio), and the PRS is calculated as a sum of the numbers of risk alleles multiplied by the respective coefficients [44].

The first PRS model for AD risk assessment was published in 2005, even before large-scale GWAS. This model includes nine SNPs, including the ε4 allele of APOE [45]. Based on the GWAS data, the PRS models were proposed and 19 to 31 SNPs were included in the most elaborated ones [46–49]. Additional factors may include APOE gene alleles, gender, age, as well as other social and physiological characteristics.

Studies of PRS models have established an association of the values of this parameter with the risk and age of AD and dementia development [48–50], as well as the rate of MCI progression and the risk of it spilling into AD [51–53]. It should be noted that cognitive functions in healthy subjects at different ages have also been shown to be associated with PRS [53–56]. Moreover, PRS has been shown to be associated with structural and functional brain abnormalities, as well as some biochemical parameters typical o neurodegeneration [48, 57, 58], including deposits of amyloid and the tau protein [59–62].

Thus, polygenic models represent a promising tool for identifying people at high risk of developing AD. From the practical viewpoint, these tests are useful in the selection of individual preventive measures and the development of screening strategies. Furthermore, PRS can be effectively deployed when designing clinical studies of AD therapy methods that may prevent progression of the disease; it is assumed that the inclusion of people with high PRS values and, accordingly, a higher risk of AD development into the evaluated cohorts may increase the chances of identifying effective prophylactic strategies [44, 62].

It should be noted that most of the studies of PRS in patients with AD were conducted on Caucasians, and that additional studies will be required to extend the obtained results to other populations [44]. This should be taken into account when using this approach for the multinational Russian population.

DISCUSSION

Diagnostic criteria for AD currently include the assessment of three classical biomarkers (T-tau, P-tau, Aβ42) in the cerebrospinal fluid. They have been the most thoroughly studied and elaborated. There is a number of promising CSF biomarkers (neurogranin, membrane protein SNAP-25, GAP43 protein etc.) which are being actively studied and have potential prognostic value. Blood biomarkers include beta-amyloids (Aβ), the tau protein, neurofibrillary tangles (NFTs), apolipoprotein E (ApoE), etc. They do not provide reliable diagnostic information when assessed separately; however, the assessment of a multiple blood biomarkers panel using mass spectrometry and machine-learning technologies appears promising. The generation of fundamental knowledge that is not oriented toward one biomarker, e.g. Aβ, allows one to use the integrative systematic approach to differentiate between normality and abnormality based on the patient's biomarker profile [63].

Researchers have demonstrated the importance of resorting to biochemical and genetic markers in laboratory diagnostics [2, 27]. Neuroinflammatory biomarkers (interleukins, TNFα, TGF-β etc.) are the most commonly detected in patients with neurodegenerative disorders; however, they suffer from low specificity. The search for specific neuroinflammatory markers and their use in patients with MCI or dementia may be crucial for understanding early stages of neurodegenerative disorders. We believe that the neuroinflammatory markers that have been evaluated to date are of significant prognostic potential and can already be used for diagnosis.

Neurodegenerative disorders are commonly associated with changes in the concentrations of neurotrophins (BDNF, NGF, etc.) and neuroinflammatory markers; however, these changes are not specific enough to enable confident diagnostic decisions. Further research is needed to identify AD-specific neurotrophic biomarkers.

Today, a number of genetic markers are used for genetic screening, primarily, APOE gene polymorphisms, the detection of which predicts the development of Alzheimer's disease with a high probability and can be used in the future for the prescription of targeted therapy. Therapeutic approaches targeting the APOE, including: 1) their effects on the structural properties of apolipoprotein E and interaction with Aß, 2) modulation of APOE levels, and prenylation, 3) the effects on APOE receptors, and 4) APOE gene therapy, are currently being developed using animal models. Moreover, some researchers believe that genetic biomarkers will contribute to a better understanding of the disease pathogenesis [53, 55]. PRS models appear promising for diagnosis and preventive medicine. From the practical viewpoint, these models should be useful in the selection of individual preventive measures and the development of screening strategies. Furthermore, PRS can be effectively used when designing clinical studies of AD therapies that may prevent progression of the disease; it is assumed that the inclusion of people with high PRS values and, accordingly, a higher risk of AD development into the evaluated cohorts may increase the chances of identifying effective prophylactic methods [44, 62]. It should be noted that most of the studies of PRS in patients with AD were conducted on Caucasians, and that additional studies will be required to extrapolate the obtained results to other populations [44]. This should be taken into account when using this approach for the multiethnic Russian population.

Strengths and limitations of the study

Our study covers different types of biomarkers, presents a brief description of their characteristics and potential uses, and includes an overview of the main research areas. The limitation of this study is that a number of suitable studies on the topic could have been missed, since no systematic search strategy was used for the purposes of this review. Therefore, the conclusions drawn in the article may be considered preliminary.

Application of the results

The improvement of diagnostic accuracy using multiple biomarkers determined using various omics technologies is one of our most immediate challenges, the solution of which will facilitate the diagnosis of cognitive impairment, increase the efficacy of therapeutic and rehabilitation measures, and improve prognosis and patients' quality of life. Another relevant issue is the development of modern diagnostic approaches based on the evaluation of a panel of neuroinflammatory and neurotrophic markers. The specific feature of these markers is potential prognostic value at the preclinical stage of cognitive impairment, when timely medical interventions can still prevent or significantly slow down the progression of cognitive decline.

CONCLUSION

The active use of biomarkers in clinical practice, in combination with genetic screening, for early diagnosis of cognitive impairment in Alzheimer's disease can increase the timeliness and effectiveness of medical intervention. However, the development of a comprehensive and effective strategy for the management of AD-associated cognitive impairment requires further research aimed at improving diagnostic accuracy using biological markers, such as neuroinflammatory markers. An important issue that needs to be addressed in the future is not only the search for new biological markers, but also their active introduction into clinical practice.

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Supplementary data

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