

The Evolution of Diagnostic Boundaries of Alzheimer's Disease and Novel Therapeutic Options

Эволюция диагностических границ болезни Альцгеймера и новые терапевтические возможности

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Review



Svetlana Gavrilova

*Mental Health Research Center,
Moscow, Russia*

Светлана Гаврилова

*ФГБНУ «Научный центр психического здоровья»,
Москва, Россия*

ABSTRACT

Over the past three decades, the definition and diagnostic boundaries of Alzheimer's disease (AD) have been repeatedly revised due to significant progress in understanding of the pathogenesis of neurodegeneration associated with Alzheimer's disease and in the development of high-tech diagnostic methods. The current approach to AD diagnostics relies on the detection of biomarkers that reflect two main neuropathological processes involved in the primary neurodegeneration that underlies AD: abnormal amyloidogenesis, and neuronal degeneration. The currently available diagnostic tools are limited to the detection of cerebrospinal biomarkers and/or assessment of the abnormal amyloid and tau protein burden in the brain via amyloid and tau positron emission tomography (PET) ligands. Practical implementation (mostly in the research field) of the biological model of AD diagnosis has led to a significant expansion of its diagnostic boundaries with the inclusion of prodementia AD stages: asymptomatic and symptomatic, the latter is clinically corresponding to amnesic mild cognitive impairment (aMCI-amnesic mild cognitive impairment). On the one hand, this approach significantly expands the possibilities to study and use preventive technologies aiming to avert or delay the progression of prodementia cognitive impairment to dementia but, on the other, it is associated with a number of negative implications from both the clinical and ethical points of view. A significant limitation of purely biological diagnosis of AD based on biomarker levels is due to the low prognostic value of biomarkers, which can cause diagnostic confusion in certain circumstances. Moreover, since the future evolution of the asymptomatic stage is not yet clear and there are still no reliable ways to prevent the cognitive and behavioral symptoms associated with AD, disclosure of stressful information about this "terrifying" diagnosis to patients can cause irreversible damage by triggering depressive disorder, which is a risk factor of AD itself.

The current knowledge about AD prognosis in amyloid-positive cognitively unimpaired patients is insufficient. The most adequate approach to early AD diagnostics appears to be the clinical and biological model, as recommended by the International Working Group (IWG 2021), which requires a combination of the clinical AD phenotype and the detection of biomarkers specific to this disease.

The article discusses the potential directions for the development of biological diagnostic methods, including those based on the so-called peripheral (serum) biomarker technologies and promising directions for the development of biological methods of secondary AD prevention.

АННОТАЦИЯ

За последние три десятилетия дефиниция и диагностические границы болезни Альцгеймера (БА) неоднократно пересматривались, что было связано с существенным прогрессом в понимании патогенетических механизмов

альцгеймеровской нейродегенерации и в разработке высокотехнологичной диагностической техники. Современный подход к диагностике БА опирается на открытие биомаркеров, отражающих два главных нейropатологических процесса, вовлеченных в развитие первичной нейродегенерации, лежащей в основе БА, — аномального амилоидогенеза и нейрональной дегенерации. Существующие сегодня диагностические технологии ограничиваются выявлением ликворных биомаркеров и/или оценкой распространенности в структурах головного мозга амилоидной и тау-патологии с помощью позитронно-эмиссионной томографии (ПЭТ) с лигандами бета-амилоида и тау протеина. Внедрение в практику (в большей мере — исследовательскую) биологической модели диагностики БА привело к значительному расширению ее диагностических границ за счет включения додементных стадий заболевания — асимптоматической (бессимптомной) и симптоматической, клинически соответствующей синдрому мягкого когнитивного ухудшения амнестического типа (aMCI-amnestic mild cognitive impairment). Такой подход, с одной стороны, существенно расширяет возможности изучения и применения превентивных технологий, направленных на предотвращение или замедление перехода в деменцию додементных когнитивных расстройств, но с другой стороны сопряжен с рядом негативных последствий клинического и этического плана. Существенным ограничением чисто биологической диагностики БА на основе определения биомаркеров является низкая прогностическая ценность биомаркерных критериев, которая может в определенных случаях создавать диагностическую путаницу. Кроме того, раскрытие стрессогенной информации о «страшном» диагнозе пациенту при том, что траектория развития асимптоматической стадии еще надежно не определена и все еще нет надежного способа предотвратить развитие когнитивных и поведенческих симптомов, связанных с БА, может нанести непоправимый вред пациенту, спровоцировав депрессивного расстройства, которое само по себе является одним из факторов риска БА.

На современном этапе неполных знаний о прогнозе развития БА у амилоид-позитивных когнитивно сохранных пациентов, наиболее адекватным подходом к ранней диагностике БА представляется клинко-биологическая диагностическая модель, рекомендуемая рабочей группой IWG 2021, которая требует сочетания клинического фенотипа БА и выявления биомаркеров, характерных для этого заболевания.

В работе обсуждаются возможные направления развития биологических методов диагностики, в том числе, в области так называемых периферических (сывороточных) биомаркерных технологий и перспективные направления в разработке биологических методов вторичной профилактики БА.

Keywords: *Alzheimer's disease; diagnostic boundaries; biomarkers; treatment; secondary prevention*

Ключевые слова: *болезнь Альцгеймера; диагностические границы; биомаркеры; лечение; вторичная профилактика*

INTRODUCTION

A global issue of the 21st century is combating socially significant diseases, including neurodegenerative diseases accompanied by dementia, primarily Alzheimer's disease (AD). AD currently affects more than 50 million people worldwide and, based on the prognosis of the World Health Organization (WHO) and Alzheimer's Disease International (worldwide federation of Alzheimer's disease associations), this number is expected to reach 150 million by 2050. The medical, social, and economic consequences of AD are expected to show a trend of exponential growth over the next few years as a result of the demographic changes currently underway in both

developed and developing countries, and will almost certainly lead to an increasing proportion of elderly and senile individuals in the population and to an inevitable increase in the number of individuals with dementia among them. Over the next 30–40 years, almost every currently living person will presumably be affected by dementia either as a patient or as a caregiver. The highest growth in morbidity is expected in low- and middle-income countries, Russia being one of the latter. The proportion of patients with dementia in these countries is predicted to increase from 58 to 71% of the global dementia population. Dementia caused by AD places a huge economic burden on a country and society in

general. In the USA alone, medical care and long-term care expenditures associated with dementia (in more than 60% of cases associated with AD) are estimated to be 355 billion dollars [1].

Despite massive investments, primarily in the global market of drugs used for the treatment of this disease, AD still inevitably leads to severe disability and death. After more than thirty years of highly active research in neurobiology and neuropharmacology, and tremendous financial expenses comparable to the annual budget of an average European country, there are still no drugs that can not only reduce the clinical severity of the disease symptoms but also reliably modify its course, i.e., stop or significantly delay its progression.

EVOLUTION OF THE VIEWS OF ALZHEIMER'S DISEASE DIAGNOSTICS

Experts in this area believe that one of the main reasons for such poor outcomes of AD treatment is the late start of therapeutic intervention. In clinical practice, AD is generally first diagnosed only at the stage of clinically apparent dementia, i.e., at the stage of advanced neurodegeneration. Therefore, there is an urgent need to develop routine methods for the diagnosis of AD at an early, predementia — or even pre-symptomatic — stage of neurodegeneration, i.e., when neuropathological abnormalities specific to Alzheimer's disease are present, but no clinical symptoms are yet manifesting. Experts estimate that this asymptomatic stage may last for at least 20 years. According to some researchers, at this earliest stage of the pathological process the maximum therapeutic effect, focused on preventing the transition from predementia cognitive impairment to dementia, can be expected. In the last decade, important progress has been made in the development of in vivo biomarkers of AD, which significantly help in both understanding the pathogenesis of this disease and determining its diagnostic boundaries. The NINCDS-ADRDA [2] diagnostic criteria were first revised in 2007. The International Working Group (IWG) led by Professor B. Dubois [3] proposed to consider AD a clinical-biological entity based on a combination of in vivo biomarkers (cerebrospinal fluid biomarkers or MRI signs of atrophy together with FDG PET hypometabolisms in certain brain areas or autosomal dominant mutations) and a specific clinical phenotype. Consequently, the definition of AD applies not only to dementia but also to the predementia stage.

In 2010, the same working group proposed the inclusion of two predementia stages, the asymptomatic and the symptomatic, within the diagnostic boundaries of AD. The asymptomatic stage applies to people with AD biomarkers in the absence of clinical manifestations. The diagnosis of symptomatic stage applies to patients who clinically meet the criteria of mild cognitive impairment (MCI) or mild neurocognitive disorder (DSM-5 terminology), and in whom AD biomarkers have been detected [4]. The diagnostic criteria were further improved in 2011. Under the auspices of the US National Institute on Aging (NIA) and the Alzheimer's Association (AA), the working group developed guidelines on the diagnosis of AD comprising two sections: the first includes a set of clinical criteria that can be used in the healthcare practice since they do not require high-technology neuroimaging studies or cerebrospinal fluid tests; the second includes a set of exploratory criteria to be used for research purposes and in clinical trials of novel drugs [5]. These exploratory criteria require mandatory detection of biomarkers using either high-technology neuroimaging methods (amyloid PET or tau PET) or cerebrospinal fluid tests in the diagnosis of AD. Depending on the presence and nature of detected biomarkers, AD criteria are divided into four levels of diagnostic certainty based on the presence of biomarkers reflecting amyloid pathology only, neuronal degeneration only, or both.

According to these new NIA-AA criteria, the diagnostic boundaries of AD encompass not only dementia and symptomatic AD but also the asymptomatic stage. Thus, the diagnosis of AD can be established before the onset of cognitive symptoms [6]. The diagnosis is based on the detection of specific biomarkers reflecting the localization and nature of Alzheimer's neurodegeneration. These include biomarkers indicating the accumulation of amyloid- β (low cerebrospinal fluid amyloid- β 42 and/or high tracer retention in amyloid PET) and biomarkers confirming neuronal degeneration (high cerebrospinal fluid tau, both total and phosphorylated) and FDG PET hypometabolism in the temporo-parietal cortex, along with signs of brain matter atrophy via structural MRI. An important limitation of these diagnostic criteria is the lack of standardized values for each biomarker. The researchers admit that some aspects of AD diagnostic criteria based on biomarker validation may require revision in the future. Presumably, such revisions will be regularly made as new information becomes available.

Although the diagnostic criteria above were intended for research purposes only, they raised controversy due to their potential extension to clinical practice, for example, if positive biomarkers are detected in cognitively unimpaired elderly and senile individuals who never develop clinical symptoms of AD throughout their lives. Problems also arise when AD biomarkers are detected in patients with a clinical presentation of another neurodegenerative disease (e.g., Parkinson's disease or Lewy body dementia), i.e., when Alzheimer's neuropathology is some form of comorbidity. The implementation of a diagnostic approach based on Alzheimer's biomarkers in practice is also problematic due to the lack of consistent biomarker thresholds. The delimitation between positive and negative patients for any given biomarker significantly varies between studies. At the same time, any changes in biomarker thresholds, e.g., as diagnostic technologies improve, will have a significant impact on both the diagnostic boundaries of AD and disease staging.

Moreover, a significant limitation of the purely biological definition and, respectively, diagnostic boundaries for AD solely based on biomarker levels is the low predictive value of biomarker-based criteria. Several longitudinal studies showed that positive AD markers in asymptomatic individuals are not sufficient to predict symptoms typical for clinical AD phenotypes, i.e., aMCI or Alzheimer's dementia.

In particular, in the INSIGHT study [7, 8], no clinical signs, either cognitive, behavioral, or neuroimaging, were observed during 5 years in 83% of amyloid-positive elderly patients (mean age at the study entry: 77 years) compared with the baseline characteristics of these patients or with a cohort of amyloid-negative individuals of the same age. The results of another prospective study (ALBA) confirmed the data above: 81% of elderly patients from a cohort of amyloid-positive individuals (mean age at the beginning of the prospective study: 75 years) also showed no cognitive decline after 6 years.

Moreover, in a large cohort of cognitively unimpaired elderly individuals (576 subjects with a mean age of 71 years), amyloid and diffuse tau pathologies were found in a quarter (24%) of subjects [9].

Other studies [10, 11] showed that similar amyloid and tau pathologies were detected via PET imaging using appropriate tracers in both cognitively unimpaired elderly individuals and subjects with mild cognitive impairment.

Moreover, biomarker-based diagnosis of AD in cognitively unimpaired elderly and senile individuals has negative ethical aspect. Telling cognitively sound individuals that they have an irreversible disease associated in public opinion exclusively with inevitable severe disability, dependency, and death will negatively affect their treatment compliance and patient-doctor interactions, aside from the potential negative psychological reaction to this "terrifying" diagnosis. Given that the future evolution of the asymptomatic stage is not yet clear and there are still no reliable ways to stop the progression of cognitive and behavioral symptoms associated with AD, disclosure of this stressful information to a patient can cause irreversible damage by triggering depressive disorder, which is a risk factor of AD itself. When Alzheimer's biomarkers are detected in cognitively unimpaired individuals, they can only be informed that they are at risk of progressive cognitive impairment rather than being diagnosed with a preclinical stage of AD. This will cause no psychological damage and can even help in discussing the strategy of preventive measures with the patient with the aim of eliminating the potentially modifiable risk factors or in discussing the benefit-to-risk ratio of the preventive treatment that is offered to the patient.

It should also be noted that AD diagnosis based on biomarker detection rather than clinical phenotype can potentially create diagnostic confusion. This is particularly true for cognitively unimpaired individuals of very old age (85 years and older), almost all of whom have subjective complaints of memory-related problems and a few signs of AD based on PET biomarker and cerebrospinal fluid testing. According to IWG-2021 [12], detection of AD biomarkers is not sufficient to reliably predict the progression of asymptomatic stage to clinical AD symptoms. The author shares this view.

According to experts, the relationship between the presence of amyloid beta and tau pathology on the one hand, and progressive cognitive decline on the other is still uncertain at the individual level [13].

However, a pressing issue in improving the AD diagnostics and a prerequisite for future use of preventive antidementia strategies in neurodegenerative diseases is finding so-called peripheral AD biomarkers, i.e., markers that can be measured in blood serum or other body fluids (urine, saliva). In contrast to those currently used, such markers do not require traumatic invasive methods

(e.g., spinal puncture) or high technology that are extremely costly and thus unavailable in general medical practice (such as amyloid or tau PET, FDG PET, etc.). It must be emphasized that the aforementioned limitations of biomarker use in routine clinical practice must equally apply to peripheral biomarkers.

A certain degree of progress in the detection of serum biomarkers has been achieved in recent years. Modern approaches (proteomics, metabolomics, mass spectrometry) have helped to discover a number of proteins, their metabolites, or combinations of several protein molecules that are assumed to be potential peripheral markers of AD [14–16]. However, to confirm the diagnostic significance and to determine the thresholds of these new biomarkers, they must be validated, including in prospective or follow-up studies. Candidates currently evaluated as possible early diagnostic markers of AD include P-glycoprotein (P-gp); microRNAs (miRNAs), and free copper ions [17].

Russian researchers have proposed the following possible diagnostic serum AD markers: low expression of amyloid degradation enzyme neprilysin [18]; changes in ratio of sphingolipids sphingomyelin and ceramide [19], anti-p75 receptor antibody levels [20], etc. Studies are currently being developed to evaluate the sensitivity, specificity, and reliability of these biomarkers for the diagnosis of AD at the prodementia stage.

From our point of view, considering the multifactorial nature of the neurodegeneration associated with Alzheimer's and its heterogeneous phenotypes, developing a multimodal panel of biomarkers appears to be more reasonable than expecting that a single biomarker that can reliably confirm the Alzheimer-related nature of cognitive decline will be discovered. AD is known to develop as a result of a combination of multiple pathogenic factors, including genetic, environmental, constitutional, somatic, and temporal factors. Heterogeneous combinations of such factors result in various AD phenotypes: familial and sporadic, presenile (early-onset) and senile (late-onset), pure and mixed, i.e., combined with other types of brain disease. Thus, a multimodal panel of biomarkers should, in theory, better reflect the complex nature of this disease, although the assessment of such data would entail a number of additional challenges and the algorithm for the analysis of their diagnostic value is yet to be developed.

In this regard, new data on the pathogenetic role of neuroinflammation in the development of AD are

of particular interest [21–23]. A correlation has been established between increased inflammatory marker levels and the severity of cognitive disorders in AD patients, as well as the progression of cognitive decline in older age. A prospective three-year study in a cohort of 252 elderly patients with aMCI showed that a low-grade systemic inflammatory response detected based on the levels of certain cytokines, tumor necrosis factor, and CRP in peripheral blood serum predicts a significant increase in cognitive decline or progression to dementia within the next three years [24]. It was also shown that such an integrative parameter as the ratio of leukocyte elastase (LE) enzymatic activity and alpha1-proteinase inhibitor (alpha1-PI) functional activity has a statistically significant correlation with the probability of AD in patients with aMCI [23]. These data served as the basis for developing the Alzheimer's disease immune test [25]. Thus, the results of recent clinical and immunological studies create new opportunities to develop a novel pathogenetic model of AD and new diagnostic approaches based on this model. However, further significant efforts are needed to validate the peripheral biomarker-based criteria and to standardize the biomarker tests before they can be used as part of patient care.

NEW APPROACHES TO DRUG THERAPY FOR ALZHEIMER'S DISEASE

An equally pressing task at present is to find effective methods of pharmacological intervention able to stop or substantially delay neurodegeneration that has already started and thus prevent or delay the onset of dementia for several years. If this issue is not solved, the ultra-early diagnosis of AD or another progressive neurodegenerative disorder leading to dementia becomes a purely scholastic activity which is not only useless to the patients but can even subject them to significant harm by causing chronic psychological stress and depression, which is in itself a risk factor of dementia in elderly individuals.

Over the last several decades, multiple — and increasingly well-designed — clinical trials have been conducted to evaluate various drugs (nonsteroidal anti-inflammatory drugs, Ginkgo Biloba, statins, estrogens, progesterone, vitamins E and C, betacarotene, folic acid, selenium, etc.) presumed to exert disease-modifying effects. Unfortunately, none of the investigated agents demonstrated reliable preventive effects, i.e., the ability to prevent or delay dementia. The anti-amyloid strategies

for AD therapy extensively investigated over the last few years in international programs using various amyloid targeting drugs have also failed to yield significant clinical results. A clear breakthrough in this regard, however, was the FDA approval of aducanumab, which is an anti-amyloid drug. It was approved for AD prodementia and mild dementia stages. Although it has a rather narrow therapeutic window, this drug opens new opportunities in the prevention or delaying dementia associated with AD, provided that treatment is initiated at the symptomatic stage, i.e., in amyloid-positive individuals with aMCI.

The analysis of previously used methods of prevention and treatment showed that in the vast majority of cases, treatment goals were aimed at blocking certain pathogenetic links of AD or mitigating the consequences of long-term neurodegeneration. However, attempts to influence the existing compensatory mechanisms in the human brain, i.e., the so-called endogenous system of brain defense and recovery were only made as part of small pilot studies. The endogenous brain defense system consists of a number of natural neurobiological processes, including neuroprotection, neurotrophic regulation, neuroplasticity, and neurogenesis, which ensure the survival of neurons exposed to certain damaging factors.

Under natural circumstances, these components of the endogenous brain defense system are regulated by natural neurotrophins such as NGF, BDNF, etc. In the last decade, neurotrophins, in particular NGF, became very promising candidates for the treatment of AD, as it was shown that low neurotrophic support plays an important role in the pathogenesis of Alzheimer's neurodegeneration. NGF prevented cholinergic neurons degeneration after experimental damage of basal forebrain septo-hippocampal nuclei and averted the progression of cognitive disorders in experimental animals. Unfortunately, natural neurotrophins cannot cross the blood-brain barrier due to the large size of the molecules, whereas low-molecular-weight synthetic neurotrophins are not yet available. Thus, studies of already approved neurometabolic drugs with demonstrated neurotrophin-like properties became a new area of clinical research. In particular, the researchers turned their attention to the long-known-about drug Cerebrolysin, which was used in the treatment of cerebrovascular diseases about half a century ago. New data are available on its biological

and clinical effects due to the biologically active low-molecular-weight peptides present in its composition, part of which are similar in structure and chemical properties to natural neurotrophins [26]. Experimental data suggest that Cerebrolysin has sustained effects on neuropathological manifestations of AD: it reduces the formation of amyloid plaques and synaptic deficit in experimental animals, increases survival and structural integrity of neurons following exposure to pathophysiological stressors [27, 28], and can prevent the degeneration of cholinergic neurons [29].

A meta-analysis of six randomized, placebo-controlled studies demonstrated significant therapeutic effects of this drug based on the assessment of cognitive functions and its overall clinical effectiveness in the treatment of mild to moderate AD [28]. The results of a relatively small (110 patients) three-year comparative, prospective, parallel group study which showed significant effects in preventing the conversion of aMCI to the dementia associated with AD in elderly patients treated with two yearly courses of Cerebrolysin therapy are of particular interest in investigating the possible preventive anti-dementia effects of this drug [30].

Moreover, a recent clinical and immunological study conducted as part of the development of a strategy of preventive therapy for dementia in elderly patients with aMCI identified immunological markers of long-term therapeutic effects of Cerebrolysin [31].

Overall, the data above regarding the role of neuroinflammation and immune response in the development of AD create new opportunities to develop methods to correct the immune response as a promising direction of secondary dementia prevention in patients with early prodementia manifestations of AD.

CONCLUSIONS

One-fifth of people aged 65 years and older are reported to have mild cognitive impairment (MCI), and the number of such patients in developed countries is steadily increasing. About one half of elderly individuals with aMCI are diagnosed as MCI associated with AD (or the prodementia stage of AD) based on biomarker measurements. This implies the progressive nature of cognitive decline and its probable conversion to dementia within the next three years. This particular category of elderly individuals can be viewed as the most accessible "window" for interventions aimed

at preventing the dementia associated with AD. The results of a few longitudinal studies indicate that preventive drug interventions such as antidiabetic or neurotrophin-like agents may reduce the rate of conversion to dementia. Therefore, the assumption that agents potentially increasing brain neuroplasticity along with anti-amyloid drugs should be used as prevention therapy appears to be promising. Experimental data confirm that several drugs, such as Cerebrolysin, citicoline, and acetyl-L-carnitine used in clinical practice for other indications, can influence endogenous brain defense and recovery mechanisms.

Considering the phenotypic and pathogenetic heterogeneity of Alzheimer's neurodegeneration, one can assume that multimodal and multicomponent preventive interventions directed at multiple causes of cognitive decline progression in individuals at risk of AD, in particular elderly people with aMCI, could help to reduce the rate of conversion to dementia. However, only the results of prospective, randomized, placebo-controlled studies in large cohorts of patients with MCI of a biomarker-confirmed Alzheimer-related nature can provide clarity in this regard.

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Information about the authors:

***Gavrilova Svetlana Ivanovna**, Professor, Doctor of Sciences in Medicine, Professor, Head of Geriatric Psychiatry Department and Division of Cognitive Disorders and Dementia of the Federal State Budgetary Scientific Institution "Mental Health Research Center", ORCID: <https://orcid.org/0000-0001-6683-0240>

E-mail: sigavrilova@yandex.ru

*corresponding author

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