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NEW MOLECULAR AND NEUROINFLAMMATORY BIOMARKERS FOR PRECLINICAL DIAGNOSIS OF NEURODEGENERATIVE DISEASES

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ABSTRACT
Nonrodegenerative diseases represent such a geterogenous group with a chronic progression of the central nervous system, characterizing the pre-clinical period and pre-clinical manifestation, which effectively restricts the possibilities of timely diagnosis and evaluative treatments. In the meantime, the presentation of pathogeneese data is published in the public domain, indicating that the key role of the pathological aggregation of Belkov, neyrovospalenia, activations of glialn pengamh cell and dysregulation of immunn wawamh mechanism, forming the basis of the nerodegenerative process, will be extended to the occurrence of clinical symptomatology. The review analyzes modern domestic and foreign studies on molecular and neuroinflammatory biomarkers used and being developed for preclinical diagnosis of neurodegenerative diseases. The amyloid, tau, and synuclein-associated markers, as well as cytokine and glial parameters reflecting various links in the neuroinflammatory response, were considered. Special attention is paid to the biomarker of spin-and-spin tests and how to make a good use of the tool in the early days of the undeclared neorodegenerative process, monitoring and evaluation of therapeutic responses. It is shown that there is no significant potential of the specificity of the specificity, the variability of the specificity, the variability of the specificity and the variability of the uniformity of the specificity of the specificity, the variability of the specificity of the specificity, the variability of the specificity of the specificity and the absence of the uniformity of the diagnostics of the specificity of the patient. There is a need for integration of biomarkern wawrabh data with clinical and non-performance evaluative evaluative indicators, and the large-scale-longitudn wawrabh is being investigated for sub-determinations and prognostic meanings. Representativeservice data; testify about the prospects of biomarker-specific approach for formations personalised; strategy and early diagnosis; and the patient with nerodegenerative diseases;

KEYWORD: neorodegenerative wawrame diseases, pre-clinical diagnosis, molecular wawrame biomarker Apostille, neorovospalenia, spinal cord gidcost, biomarker Apostille.

INTRODUCTION
Neurodegenerative diseases are a heterogeneous group of chronic progressive lesions of the central nervous system, which are based on selective loss of neurons and disruption of intercellular signaling mechanisms, which determines their leading role in the structure of modern neurological pathology [1]. In recent years, these diseases have acquired pronounced medical and social significance, as they are accompanied by an increase in the life expectancy of the population, an increase in the number of patients with cognitive and motor impairments, and a significant burden on healthcare systems [2-5]. According to the World Health Organization, there are more than 55 million people worldwide suffering from dementia and related neurodegenerative disorders, with a further increase in the incidence predicted in the coming decades [6].
A similar trend is observed in the Russian Federation, where, according to official statistics from Rosstat and the Ministry of Health, there is a steady increase in the number of patients with Alzheimer's disease and Parkinson's

disease, while the true prevalence of these conditions is probably significantly higher due to late diagnosis [7]. A significant problem lies in the fact that the clinical manifestations of neurodegenerative diseases are formed after a long latent period, when pathological molecular and cellular changes in the nervous tissue are already irreversible. In this context, the search for new molecular and neuroinflammatory biomarkers that can detect the neurodegenerative process at the preclinical stage becomes particularly relevant [8]. Modern concepts of the pathogenesis of these diseases point to the leading role of pathological protein aggregation, chronic neuroinflammation, activation of glial cells and oxidative stress, which creates prerequisites for the use of appropriate biochemical and immunological parameters as diagnostic markers.

In this regard, it seems necessary to comprehensively summarize modern concepts of molecular and neuroinflammatory biomarkers used and being developed for preclinical diagnosis of neurodegenerative diseases, since the available information is fragmentary and often based on heterogeneous methodological approaches [9-15]. The insufficient comparability of the results of various studies, as well as the limited number of papers devoted to assessing the clinical reproducibility and prognostic significance of such markers, significantly complicate their practical use [16-20]. These circumstances determine the need for a generalized analytical review and further targeted research aimed at systematization and in-depth study of molecular and neuroinflammatory biomarkers of neurodegenerative diseases.

The purpose of the review is to summarize and analyze current data on new molecular and neuroinflammatory biomarkers for the preclinical diagnosis of neurodegenerative diseases and to assess the prospects for their clinical application.

MATERIALS AND METHODS

This review is based on a systematic analysis of domestic and foreign scientific publications devoted to the study of molecular and neuroinflammatory biomarkers of preclinical diagnosis of neurodegenerative diseases. Literary sources were searched in international and national electronic databases PubMed, MedLine, Web of Science, Scopus, as well as in Russian scientific resources. eLIBRARY.RU .

The analysis included full-text original research, systematic reviews, and meta-analyses published primarily in English and Russian. The time frame of the search covered a period of up to 20 years, which made it possible to trace the evolution of ideas about the pathogenetic role of molecular and neuroinflammatory markers in neurodegenerative diseases. The main criteria for inclusion were: compliance with the review topic, availability of data on biomarkers of cerebrospinal fluid and/or blood, as well as analysis of their diagnostic and prognostic significance at preclinical stages of diseases.

The search strategy was based on the use of the following keywords and their combinations: neurodegenerative diseases, preclinical diagnostics, molecular biomarkers, neuroinflammation, amyloid, tau protein, α-synuclein, cytokines, glial markers, cerebrospinal fluid, blood biomarkers, microRNAs, exosomes. Additionally, links in selected publications were analyzed to identify relevant sources that were not included in the primary search.

Abstracts of conferences, individual clinical observations, methodological recommendations, textbooks and publications without an accessible full text were excluded from consideration. The assessment of the relevance of sources was carried out in two stages: based on the analysis of annotations and after studying the full text of publications. The selection of literature and the synthesis of data were carried out taking into account the principles of systematic reviews, with a focus on the recommendations of PRISMA (2020) on transparency and reproducibility of scientific analysis.

Neurodegenerative diseases in the practice of modern neurology: pathogenetic prerequisites for preclinical diagnosis

Neurodegenerative diseases in modern neurological practice are considered as a heterogeneous group of chronically progressive conditions based on the gradual and irreversible loss of neurons, leading to atrophy of functionally significant brain structures. In this context, clinically and pathogenetically, this group includes Alzheimer's disease, Parkinson's disease, Huntington's chorea, frontotemporal degeneration, amyotrophic lateral sclerosis, and dementia with Lewy bodies, which, with pronounced phenotypic differences, are united by similar molecular mechanisms of neurodegeneration [20-25].

With all the variety of clinical forms, most of these diseases are characterized by a combination of cognitive decline, motor disorders, and progressive limitations of social adaptation, which makes it possible to consider them not as isolated syndromes, but as systemic pathological processes [26-28]. This understanding is the basis of the modern neurological concept, according to which, by the time of the clinical manifestation of the disease, the pathological process has been developing for a long time in the preclinical phase, which fundamentally changes approaches to early diagnosis [29-35].

Within the framework of this approach, pathogenetic research is of particular importance, in particular the work of I.V. Litvinenko et al. [2], which emphasize the key role of proteotoxic stress, neuroinflammation and disorders of cellular degradation systems as universal prerequisites for neurodegeneration. At the same time, the authors point out that the practical translation of these concepts into clinical diagnostics remains limited, which preserves the gap between fundamental knowledge and their applied use.

A similar problem is revealed by the research of S.N. Illarioshkin and colleagues [8], demonstrating that the latent stage of the neurodegenerative process can be detected long before the onset of clinical symptoms, however, the markers currently available lack sufficient specificity for confident individual diagnosis. In this context, modern biomarkers, including plasma p-tau217, microRNAs, and circular RNAs, are actively discussed, which indicate a high sensitivity of molecular changes in the early stages of neurodegeneration, but are characterized by significant variability in results and the lack of unified diagnostic thresholds.

The prospects of this approach are confirmed by the studies of Mattsson-Carlgren et al., who showed the informative value of dynamic monitoring of biomarkers in Alzheimer's disease, however, the authors themselves emphasize the need for long-term longitudinal observations for their clinical validation [36-38]. Complementing these data, the analysis of the role of microRNAs in neurodegenerative diseases presented in the works of van den Berg [18] and Siedlecki-Wullich [19] expands the understanding of the molecular mechanisms of synaptic dysfunction, but at the same time reveals significant technical and methodological limitations of their introduction into routine practice.

Taken together, the presented data allow us to consider neurodegenerative diseases not as local lesions of individual brain structures, but as systemic disorders with a multilevel pathogenesis that begins long before clinical manifestations [38-40]. Despite significant progress in the study of pathogenetic mechanisms, modern neurology still lacks reliable in vivo markers that can accurately diagnose a specific disease at the preclinical stage. Thus, the further development of preclinical diagnostics of neurodegenerative diseases requires the integration of molecular, neuroimaging and clinical data, as well as a critical reassessment of existing approaches from the perspective of their real applicability in the practice of modern neurology.

Neurologically significant molecular biomarkers of proteinopathies: amyloid, tau, and synuclein-associated markers

The understanding of molecular biomarkers of neurodegenerative diseases in modern neurology is formed at the junction of fundamental and clinical experimental research, which is clearly reflected in the contributions of both domestic and foreign authors. In particular, in the work of E.S. Taskina, I.V. Kibalina, V.A. Mudrova and S.O. Davydova [3] focuses on cerebral markers of neuroinflammation and neurodegeneration, which allows us to consider proteinopathies not only as a result of the accumulation of aberrant proteins, but also as a process closely related to immune and inflammatory reactions that modify the course of neurodegeneration. This expansion of the pathogenetic framework logically complements the review by F.A. Yusupov and A.A. Yuldasheva [1], which systematizes data on amyloid, tau, and synuclein-associated biomarkers, emphasizing their potential diagnostic value in the preclinical phase while recognizing the limited specificity of most of them.

In foreign studies, this problem is further developed through the analysis of peripheral markers. Thus, Wu, Kong, and Wang [20] demonstrate the relationship of blood immune factors with cerebrospinal fluid parameters of Alzheimer's disease, which reinforces the idea of the systemic nature of the neurodegenerative process and the possibility of reflecting cerebral pathology in the peripheral circulation. These findings echo the work of Toombs and Zetterberg [21], who consider plasma biomarkers of amyloid pathology and neurodegeneration as a promising, but not yet sufficiently standardized tool that requires careful implementation in clinical practice.

The population data presented by Lopez and co–authors [22] complement this concept, showing a correlation between the level of Aß1-42 in the blood and amyloid accumulation in the brain, but at the same time emphasizing that peripheral markers do not always accurately reflect the stage and severity of the pathological process [41-43].

The methodological limitations of biomarker studies are described in detail in the work of Barkovits and colleagues [23], where it is shown that even minimal contamination of cerebrospinal fluid with blood can significantly distort the quantitative assessment of α-synuclein, which is of fundamental importance for the diagnosis of synucleinopathies.

Collectively, the contributions of these authors form a holistic but ambiguous view of neurologically significant molecular biomarkers of proteinopathies, demonstrating both their high diagnostic potential and the continuing limitations associated with variability of indicators and methodological difficulties [44-45]. This highlights the need for further integration of molecular, immunological and clinical data with a critical assessment of their actual applicability in the practice of modern neurology.

The role of neuroinflammation in the progression of neurodegenerative diseases: cytokine and glial biomarkers in neurology

The increase in life expectancy in modern societies is accompanied by a steady increase in the prevalence of neurodegenerative diseases, which makes the problem of neuroinflammation central to modern neurology. Epidemiological estimates show that the expected multiple increase in the number of dementia patients underscores the systemic nature of neurodegeneration and the need to rethink its pathogenetic foundations, including the role of inflammatory mechanisms [46]. In the works devoted to Alzheimer's disease, Parkinson's disease and multiple sclerosis, the authors agree that with the clinical diversity of these conditions, they are united by progressive loss of neurons, closely related to the chronic activation of immune processes in the central nervous system [48-50]. At the same time, the studies of Yusupov and Yuldashev [1] emphasize that neuroinflammation

is not a secondary background of degeneration, but acts as an active factor influencing the speed and direction of the pathological process.

A significant contribution to understanding this problem is made by the work of Taskina et al. [3], demonstrating that activation of glial cells and changes in the cytokine profile reflect not only neurodegeneration, but also the degree of systemic immune imbalance, which is especially evident in a combination of neurological and somatic conditions. At the same time, foreign studies by Wu et al. [20] emphasize the association of peripheral cytokines with changes in cerebrospinal fluid biomarkers, however, their data indicate limited specificity of individual molecules in isolated use. Similarly, Toombs and Zetterberg [21], analyzing plasma markers of amyloid and neurodegenerative pathology, show a high diagnostic potential of such indicators, but note the dependence of the results on the stage of the disease and methodological differences between studies.

Special attention is paid to glial biomarkers, primarily microglia and astrocytes, whose role in the progression of neurodegeneration is revealed as dual - from a protective reaction in the early stages to a factor of chronic damage during prolonged activation. The work of Lopez et al. [22] demonstrate that inflammatory changes can precede pronounced amyloid pathology, however, the authors emphasize the need for careful interpretation of these data in clinical practice. At the same time, Barkovits and colleagues [23] point out the methodological limitations of the analysis of cerebrospinal fluid markers, including the effect of blood contamination, which reduces the reproducibility of the results and requires standardization of approaches. In this context, the presentation of cytokine and glial biomarkers in the form of a systematic table 1 allows us to visually compare their diagnostic value, biological role and limitations of use, which facilitates a critical assessment of their potential in the practice of modern neurology.

Table 1: Cytokine and glial biomarkers of neuroinflammation in neurodegenerative diseases

Biomarker	A source	Type of biomarker	The connection with neurodegeneration	Diagnostic significance	Main limitations
IL-1β	Microglia	Cytokine	Increases neuroinflammation and tau pathology	An early marker of inflammatory activity	Low specificity
TNF-α	Microglia, astrocytes	Cytokine	Associated with neuronal death	Correlates with the severity of the disease	We depend on systemic inflammation
IL-6	Glia, periphery	Cytokine	Supports chronic inflammation	A predictive marker	High variability
GFAP	Astrocytes	Glial protein	A marker of astrocytic activation	High sensitivity in AD	Age dependence
sTREM2	Microglia	The soluble receptor	Reflects microglial reactivity	Promising for the preclinical stage	Lack of unified thresholds
CXCL12	Immune cells	Chemokine	It is associated with the infiltration of immune cells	An additional inflammatory marker	Limited specificity
NfL	Neurons	Structural protein	Reflects neuronal damage	A universal marker of degeneration	Does not distinguish between nosologies

The information presented in Table 1 shows that cytokine and glial biomarkers reflect different links of the neuroinflammatory process and have different diagnostic value. In this context, the analysis of biomarkers of cerebrospinal fluid and blood is of particular interest, since these sources of biological material are the most accessible for clinical diagnosis and dynamic monitoring of neurodegenerative diseases.

Biomarkers of cerebrospinal fluid and blood in the neurological diagnosis of neurodegenerative processes

Biomarkers of cerebrospinal fluid and blood in the neurological diagnosis of neurodegenerative processes have been considered in recent years as one of the most dynamically developing areas of clinical neurology, due to their potential for early detection and monitoring of diseases. A number of authors emphasize that the emergence of reliable plasma markers of amyloid and tau pathology, including Aß peptides and phosphorylated tau, has become a qualitative step forward compared with the exclusively clinical assessment, but their diagnostic value still needs to be clarified in real practice [51-55]. Studies on non-specific markers of neuronal damage, such as the neurofilament light chain (NfL) and β-synuclein, demonstrate a high sensitivity to neurodegeneration in general, but at the same time indicate their limited ability to distinguish between individual nosological forms. Similarly, glial markers, in particular GFAP, according to a number of reviews, reflect astrocytic activation and neuroinflammation well, but their interpretation is complicated by the influence of age and concomitant conditions [46].

Both domestic and foreign researchers, whose work you mentioned earlier, have contributed to the formation of modern ideas about biomarkers of cerebrospinal fluid and blood in the diagnosis of neurodegenerative processes. So, in the reviews of McGrowder et al. [34], Doroszkiewicz, Groblewska, and Mroczko [35], as well as Frisoni et al. [36] consistently show the evolution of the biomarker approach in Alzheimer's disease from individual indicators to integrative models, while the authors critically emphasize the limitations of reproducibility and standardization of methods.

The analysis of neuropathological and neuroinflammatory mechanisms presented in the works of Serrano-Pozo, Das and Hyman [37] complements the biochemical approach, linking changes in cerebrospinal fluid and plasma markers with glial activation and progression of pathology. Studies by Tiwari et al. [38], as well as Zhang et al. [41], focus on new technological platforms and multiomic strategies, pointing out their prospects, but at the same time noting the gap between experimental data and clinical practice. Works by Riondo (Arriondo) et al. [39] and Zhuo, Huang, and Wu [40] expand the clinical context by demonstrating the importance of biomarkers for early diagnosis and stratification of patients, but emphasize the need for long-term longitudinal studies to confirm their prognostic value.

Prospects for the introduction of molecular and neuroinflammatory biomarkers into clinical neurology and early detection of neurodegenerative diseases

Currently, more and more attention is being paid to the prospects of introducing molecular and neuroinflammatory biomarkers into clinical neurology as tools for early detection of neurodegenerative diseases [17]. This interest is associated with a gradual shift in emphasis from exclusively clinical diagnostics to the use of biological indicators reflecting real pathogenetic processes in the nervous system. In a systematic review by Heneka et al. [55] showed that neuroinflammatory biomarkers of cerebrospinal fluid and blood are indeed associated with the stages of Alzheimer's disease, however, the authors emphasize the significant variability of the data obtained and the lack of uniform diagnostic thresholds, which limits their direct application in clinical practice.

Special attention is paid in the work of Heneka et al. [55] focuses on glial markers reflecting the activation of microglia and astrocytes, which potentially allow detecting the pathological process at the preclinical stage. However, the authors rightly point out that these indicators are sensitive to systemic inflammation and age-related changes, which requires caution in their interpretation. A practical continuation of this topic is presented in the review by Agnello et al. [53], where molecular biomarkers of neurodegenerative diseases are considered as part of a comprehensive diagnostic approach, rather than as an independent tool. The authors emphasize that the use of biomarkers without taking into account the clinical picture and neuroimaging data may reduce diagnostic accuracy.

In clinical practice, the introduction of such biomarkers opens up the possibility of stratifying patients by risk of progression, monitoring disease activity, and evaluating response to therapy [55]. This is particularly important in the context of the appearance of drugs that modify the course of the disease, the effectiveness of which directly depends on the stage of the pathological process. At the same time, the use of less invasive blood biomarkers creates prerequisites for widespread screening and dynamic follow-up, reducing the need for repeated invasive interventions [47].

Thus, the prospects for the introduction of molecular and neuroinflammatory biomarkers are associated with the formation of a new paradigm in neurology focused on early detection, personalized diagnosis and pathogenetically based management of patients with neurodegenerative diseases. Despite the remaining methodological and interpretative limitations, further standardization and integration of these markers into clinical algorithms seem to be a key direction in the development of modern neurological science and practice.

CONCLUSION

Neurodegenerative diseases are among the most complex and socially significant pathologies of modern neurology, due to their progressive course, late clinical manifestation and limited possibilities of etiotropic therapy. The data presented in the review convincingly show that the pathological process in these diseases begins long before the onset of clinical symptoms and is accompanied by complex molecular and neuroinflammatory changes, including aggregation of abnormal proteins, activation of glial cells, and dysregulation of immune mechanisms.

An analysis of domestic and foreign studies indicates that molecular and neuroinflammatory biomarkers, including amyloid, tau, and synuclein-associated indicators, as well as cytokine and glial markers, are highly promising for preclinical diagnosis and monitoring of neurodegenerative processes. At the same time, it is emphasized that most of them are characterized by limited specificity, significant interindividual variability and dependence on methodological conditions, which makes it difficult to interpret them unambiguously in clinical practice.

Biomarkers of cerebrospinal fluid and blood are of particular importance, as they allow us to approach an objective assessment of pathogenetic processes in vivo and potentially expand the possibilities of early detection of the disease, stratification of patients and assessment of response to therapy. However, the introduction of such markers requires further standardization of analytical methods, determination of diagnostic thresholds, and confirmation of their prognostic significance in large-scale longitudinal studies.

Thus, the development of preclinical diagnostics of neurodegenerative diseases based on molecular and neuroinflammatory biomarkers should be considered as one of the key areas of modern neurology. The comprehensive integration of biomarker data with clinical, neuroimaging, and neuropsychological indicators can contribute to the formation of more accurate diagnostic algorithms and create prerequisites for a personalized approach to patient management. Further research in this area has the potential not only to improve diagnosis, but also to develop new strategies for the prevention and pathogenetically based therapy of neurodegenerative diseases.

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Contribution of the authors
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