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Does new knowledge allow to improve the diagnosis of mental disorders: the problem of anti-NMDA receptor encephalitis?

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ABSTRACT

A narrative review of research studies discusses the clinical features, differential diagnosis, and treatment of anti-NMDA receptor encephalitis. Special attention is given to the controversial aspects of the etiology and pathogenesis of this disorder. The need for further research into on the role of antibodies to NMDA receptors in the development of psychiatric disorders is emphasized.

Keywords: psychosis; affective disorders; antibodies; autoimmune diseases; autoimmune encephalitis.

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Позволяют ли новые знания улучшить диагностику психических расстройств: проблема анти-NMDA-рецепторного энцефалита

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АННОТАЦИЯ

В нарративном обзоре научных исследований рассмотрены вопросы клинической картины, дифференциальной диагностики и лечения анти-NMDA-рецепторного энцефалита. Специальное внимание уделено дискуссионным аспектам этиологии и патогенеза данного заболевания. Подчёркнута необходимость дальнейших исследований роли антител к NMDA-рецепторам в развитии психических расстройств.

Ключевые слова: психоз; аффективный расстройства; антитела; аутоиммунные заболевания; аутоиммунный энцефалит.

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ЭКО•ВЕКТОР

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Яңа белемнәр психик тайпылышлар диагностикасын камилләштерергә мөмкинлек бирәме: анти-NMDA-рецептор энцефалиты проблемасы

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Аннотация

Фәнни тикшеренүләргә ясалган әлеге күзәтүдә анти-NMDA-рецептор энцефалитының клиник картинасы, дифференциаль диагностика һәм дәвалау мәсьәләләре яктыртыла. Әлеге авыруның этиологиясе һәм патогенезының бәхәсле аспектларына махсус игътибар бирелә. Психик тайпылышлар үсешендә антитәнчекләрнең NMDA рецепторларына карата ролен тикшерү киреклеге ассызыклана.

Төп сүзләр: психоз, аффектив тайпылышлар, антитәнчекләр, аутоиммун авырулары, аутоиммун энцефалит.

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INTRODUCTION

In Russian psychiatry, there is currently a crisis in the perception of approaches to the analysis of scientific data by different generations of specialists. Young colleagues are "infected with the virus" of misunderstood evidence-based medicine. They do not have basic knowledge in clinical epidemiology and interpret simplistically and sometimes incorrectly the results of randomized controlled trials, systematic reviews, and meta-analyses and clinical guidelines and algorithms for the diagnosis and treatment of mental disorders, which, with unformed medical judgment, leads to decreased efficiency of providing mental health care to patients.

Old school leaders with clinical experience often complain about the lack of basic clinical approaches among young colleagues and their underestimation of the features of the clinical presentation in an individual patient and inability to perform differential diagnostics based on the nuances of symptoms and compose a complete presentation of the pathological process in all the variety of its details from individual manifestations of the disease. Moreover, the older generation of specialists has a skeptical attitude toward research based on the principles of evidence-based medicine and use of quantitative methods for analyzing symptoms based on the use of psychometric tools. Even when clinical epidemiological approaches are used by these specialists in scientific studies, the results obtained with their help are accurate, an addition to the "true scientific" clinical method from their point of view.

Such studies often have prepossession of the material presentation and selective references to literary sources, juggling with the classic symptom names and those coined by authors (the authors themselves are often not aware of the presence of symptoms named after them). The peculiarity of such "schools" is that they exist in their own "bubble", denying or ignoring other standpoints and concepts. The discussion of literary sources in these cases is fragmented (only works that confirm the author's main ideas are selected, and the others are simply ignored). There is no systematic analysis of the literature in such cases.

Obtaining new knowledge (which is the main goal of science) in such conditions is complicated, as either long-known truths are successfully confirmed during "evidence-based research" or everything new is reduced to "old" descriptions, often starting with Hippocrates or the classics of the latter half of the 19th century and early 20th century[1]. However, new facts are emerging and require comprehension, considering both the traditional clinical approach and modern methods of evidence-based medicine.

One of these new facts is the emergence of data on the association between acute psychopathological symptoms and increased levels of autoantibodies to N-methyl-D-aspartate (NMDA) receptors. The discussion on this issue is characterized by a wide range of opinions having distinct features of the contradictions described above.

On the one hand, clinical descriptions of these conditions are often basic, which does not allow making substantiated conclusions about the structure of the syndrome and its features and dynamics, often combining manifestations that are similar only in external signs into one group without considering the mechanisms of their development and attribution to various psychopathological conditions (e.g., behavioral, speech, and sleep disorders).

On the other hand, some Russian psychiatrists deny the independence of these conditions and attempt to reduce them to already known nosological units with references to clinical descriptions of the classics of psychiatry and immunological studies in the late 20th century. Both approaches appear to have imperfections, and the facts described require special analysis.

ANTI-NMDA RECEPTOR ENCEPHALITIS

In 2005, Dalmau et al. described four cases of paraneoplastic encephalitis that developed in women with ovarian teratoma, in which clinical presentation included severe psychopathological symptoms and respiratory failure [1]. After 2 years, the authors proved the autoimmune nature of the disease associated with the production of autoantibodies to NMDA receptors [2].

A systematic review showed that between January 1, 2011, and December 31, 2021 (i.e., for 11 years), 472 cases of anti-NMDA receptor encephalitis (ANMDARE)[2] have been reported in 313 articles in English and Chinese [3]. Thus, the condition is relatively rare (1.5 cases per 1 million population [4]), which does not allow for full-scale randomized clinical trials; however, a systematic analysis of individual cases enables to consider the clinical presentation in sufficient detail, as well as the differential diagnostic criteria, therapeutic approach, and prognosis of this disease.

Based on the results of the above systematic review [3] and of a review of descriptions of ANMDARE with a predominance of psychopathological symptoms without gross neurological disorders (73 English language publications, including 79 cases of the disease with relatively detailed descriptions of patient conditions) [5], the following conclusions regarding its clinical manifestations can be drawn. In more than 3/4 of cases, ANMDARE develops in female patients, mostly young women. In most cases, the onset of disorders occurs

[1] In these cases, the extensive knowledge of the authors of such publications often dominates the content, so that the facts presented are only indirectly related to the content of the problem under discussion.

[2] The number of publications exceeded the specified number; however, cases with incomplete descriptions and descriptions of insufficient quality were excluded.

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at age 18–45, which is mainly true for women. According to a systematic review [3], the disease develops more often before age 18 in men.

A tumor was detected in half of the patients (at age 18–45, neoplasms were diagnosed in 2/3 of cases); it was most commonly ovarian teratoma (96.6%), and in isolated cases, it was mediastinal tumor, neuroendocrine uterine cancer, testicular teratoma, plasmacytoid cystic teratoma, and carcinoma [3].

Majority of the patients (~90%) experienced prodromal symptoms within 2 weeks before the acute manifestation, most often (more than half of the cases) influenza-like manifestations (e.g., headache, fever, nausea, vomiting) [3, 5].

The clinical presentation after the disease manifestation (and in some cases, at the prodromal stage) was determined by psychopathological manifestations, which often led to erroneous diagnosis. This was further facilitated by the presence of a history of mental disorders (schizophrenia/schizoaffective disorder in 5.8% of cases, bipolar affective disorder in 5.0%, depressive episodes in 3.8%, etc.) in some patients (~20%) [5].

Almost half of the patients were hospitalized within 1 week and 3/4 within 1 month after disease onset. The most common diagnoses upon admission were acute polymorphic psychotic disorder, postpartum psychosis, schizophrenia, schizoaffective disorder, delusional disorder, and bipolar affective disorder and a depressive episode. In over 90% of cases, psychotic symptoms (delusional, hallucinatory, hallucinatory–delusional) were noted. Moreover, almost 60% of patients had catatonic manifestations, more than 50% had affective disorders of both poles, and approximately 33% had gross memory impairment up to congrade amnesia and severe (sometimes reaching complete disintegration) disorders of thinking and speech [5]. It should be noted that, in addition to the detailed presentation of the disease, its subclinical forms are possible.

Generally, it is recommended to perform a differential diagnostic of ANMDARE in patients with new-onset psychotic symptoms, even in the absence of neurological signs [3, 5]. The latter most often manifest as dyskinesias and convulsive attacks, which can develop at any stage of the disease.

Magnetic resonance imaging reveals changes in at least a third (according to some data, half) of patients [3, 6]. They are characterized by dim foci of hyperintense signal of varying localizations (the hippocampus, cerebellum, cerebral cortex, basal parts of the frontal lobe, temporal and insular lobes, basal ganglia, brain stem and, infrequently, spinal cord) [3].

Pathological signs on the electroencephalogram are detected in most patients (>80% of cases). Most of them are nonspecific in nature, such as disorganization of bioelectrical activity, increased beta activity, and the appearance of slow rhythms. Epileptiform activity is less commonly (15% of patients) registered; in some cases (7%), the delta burst pattern that is characteristic of ANMDARE occurs [6, 7]. Almost 80% of patients show pathological changes in the cerebrospinal fluid (CSF), characterized by mild lymphocytic pleocytosis, increased protein levels, and emergence of oligoclonal immunoglobulin G.

A lifetime diagnosis of ANMDARE is established by the presence of autoantibodies to NMDA receptors in biological fluids (CSF, blood serum). A systematic review and meta-analysis on the clinical significance of detecting autoantibodies in biological media demonstrated that in 42% of cases, they were detected in both the CSF and blood, whereas in the remaining cases, they were found in only one of them (in CSF in 13% of cases, in the blood serum in 45% of cases) [8]. Thus, contrary to the belief that the study of the level of autoantibodies to NMDA receptors in the CSF is more informative, when blood serum is used as a biological material, autoantibodies are detected in 87% of cases compared to 55% in the CSF.

The main treatment methods for ANMDARE are immunosuppressive therapy, intravenous administration of glucocorticoids and immunoglobulins, and plasmapheresis [3]. Antipsychotic treatment is poorly tolerated with a high risk of occurrence of extrapyramidal side effects and neuroleptic malignant syndrome. If psychomotor agitation or persistent psychotic symptoms should be relieved, prescribing antipsychotics with a sedative effect and a low risk of extrapyramidal symptoms is acceptable [6]. In the presence of catatonic symptoms, benzodiazepine tranquilizers may be used.

According to a systematic analysis of clinical cases, in 35% of ANMDARE cases, complete recovery occurred, and in another 50% of patients, “significant improvement” was observed [3]. However, in 10.6% of patients, the improvement was “limited”, and in 4.4% of cases, the disease was fatal. A systematic review of clinical cases with a predominance of psychopathological symptoms without gross neurological disorders and convulsive attacks revealed a more favorable prognosis, when 61% of patients achieved complete or almost complete recovery — they returned to their previous level of functioning and continued work or study, although in some cases this required a long recovery period, taking up to a year [5]. In 30.6% of patients, residual manifestations persisted, such as cognitive impairment, affective fluctuations, suspiciousness, and fragmentary ideas of attitude.

Despite numerous indications of cognitive impairment in patients after ANMDARE, a systematic analysis in the PubMed, MEDLINE, Scopus, and Web of Science databases using the keywords “anti-NMDA” and “cognition” revealed only 15 publications describing the condition of 151 patients, using a standard set of techniques for assessing cognitive functions [9].

The data obtained were ambiguous; however, in most cases, after the patients recovered, their cognitive functioning was restored to normal levels, although some functions (i.e., working memory and attention) were more vulnerable than others, revealing some deficits in patients with already resolved neurological and psychopathological symptoms.

It was noted that in the active phase of the disease, there was a total disruption of mental activity involving all parts of the brain, but functioning of the frontal parts, primarily those responsible for working memory, was affected the most.

A 2018 systematic review, which used broader inclusion criteria (assessment at early stages of recovery, use of single nonspecific tests such as intelligence quotient test IQ), analyzed the cognitive status of 109 patients from 16 countries (44 publications) [10]. Quantitative methods were used to assess neurocognitive deficits, without attempting to group them into a neuropsychological syndrome[3]. Deterioration in at least one cognitive function was detected in 76.5% of patients, with the key deficits being deterioration of episodic memory and executive function, and, to a lesser extent, attention and information processing rate were affected.

DISCUSSION

Currently, several autoimmune encephalitis (AE) conditions have been described, owing to the presence of autoantibodies to intra- and extracellular agents (synaptic receptors, ion channels, and other surface proteins of brain cells) [11]. AE with antibodies to intracellular agents in majority of cases (except for GAD6[4] antibodies) are associated with neoplasms. AE with antibodies to extracellular agents are less often caused by cancerous diseases, although in these cases, neoplasms are commonly detected. Among AEs caused by the presence of antibodies to extracellular agents, ANMDARE, associated with the presence of antibodies, is distinct to the NR1/NR2 subunits of NMDA receptors, which is one of the most studied and frequently detected AEs.

The symptoms of AE often firs occur and/or proceed in the form of mental disorders, and patients with these diseases are referred to a psychiatrist for follow-up and treatment [11]. With ANMDARE, psychopathological (including psychotic) symptoms, usually recorded at the onset of the disease, occur in most patients [12, 13]. In 4%–5% of cases, the disease can occur in the form of an "isolated psychotic episode" [14]. In this regard, the question arises about the possibility of distinguishing "primary" psychopathological disorders from phenomenologically similar conditions, and in their pathogenesis, antibodies to NMDA receptors are significant [15, 16].

As mentioned previously, the clinical presentation of ANMDARE is polymorphic and often resembles the cycloid psychoses of Karl Leonhard, who, continuing the scientific direction of Wernike[5] and Kleist, in his taxonomy of endogenous psychoses, placed them between manic–depressive psychosis and nonsystemic schizophrenia [17]. Describing excited-inhibited confusional insanity, Leonhard emphasized a thought process disorder as the main disorder in this condition, where at the height of excitement, thinking becomes incoherent, such as the speech flow; in the "inhibition phase" (stupor), it "stops", accompanied by mutism, and false recognitions, delusions of meaning, relationships, and hallucinations may occur.

Leonhard differentiated these conditions from another variant of cycloid psychosis, namely, hyperkinetic–akinetic motor psychosis, within which disturbances in expressive and reactive movements occurred ("a psychomotor form of excitation and inhibition with circular oscillations between both poles").

Japanese authors in the mid-20th century identified similar conditions as "atypical psychosis", characterized by an acute onset (often accompanied by increased body temperature), a monophasic or polyphasic course, and impaired consciousness with psychomotor disorders [18–20].

Notably, the descriptions presented are very similar to those that are possible for psychoses within ANMDARE. Moreover, according to Leonhard, cycloid psychoses resolve spontaneously and do not induce personality changes. This indicates significant differences between cycloid psychoses in accordance with Leonhard's theory and the clinical presentation with ANMDARE with high mortality, the possibility of residual symptoms, and cognitive impairment. Several modern authors, based on a systematic analysis of literary data, indicate that if patients have psychotic symptoms that are phenomenologically similar to cycloid psychoses, a differential diagnosis with ANMDARE is required, including determining the titer of antibodies to NMDA receptors [18, 21].

When analyzing the abovementioned data, significant aspects should be kept in mind. Antibodies to NMDA receptors can be present in people who currently do not have mental disorders [22, 23], and their presence, as shown by the results of a survey of 7000 people, is not an unambiguous predictor of the disease development [23]. In a number of cases, an increased titer of antibodies to NMDA receptors was detected in people with a history of ANMDARE (albeit in a lower titer than in the acute phase of the disease) even after relief of symptoms and during the period of remission [24, 25].

Such "paradoxes" are not uncommon in medicine. For example, it is now well-established that *Helicobacter pylori* plays a significant role in the etiology of gastric ulcers; however, majority (up to 90%) of carriers of this bacterium do not have any manifestations of the disease. The causes of this phenomenon are discussed in detail by Davydovsky [26].

Thus, the presence of an elevated titer of antibodies in the blood alone is not sufficient for the development of

[3] In the work of Russian authors cited above [9], an attempt was made to perform a syndromic analysis of the identified disorders.

[4] GAD-glutamic acid decarboxylase.

[5] Wernike was one of the most irreconcilable critics of the concept of Kraepelin, who created a taxonomy of mental disorders on a linear dichotomy of two polar, from his point of view, diseases, namely, schizophrenia, characterized by a debilitating progressive course, and manic–depressive psychosis with a periodic course that does not lead to dementia.

ANMDARE. However, this does not lead to the conclusion that this disease is an artifact of scientific research. The authors of a large study mentioned previously, which obtained results indicating the possibility of detecting antibody titers to NMDA receptors without clinical signs of mental pathology [23], emphasized their great diagnostic and therapeutic value in cases of already developed disease.

Additional conditions are crucial for ANMDARE to occur. Some studies indicated the role of damage to the blood–brain barrier (BBB) in the disease pathogenesis [27–29]. However, it should be noted that ANMDARE can develop when the BBB is intact (impaired BBB permeability was detected in only 27.4% of hospitalizations for ANMDARE; however, in 24.5% of patients with an intact BBB, antibodies to NMDA receptors were detected in CSF) [27, 29]. Furthermore, it was found that when BBB integrity is impaired, the disease is usually more severe and is accompanied by impaired consciousness.

The effect of antibodies circulating in the peripheral circulatory system on the central nervous system with an intact BBB remains unclear. The presence of antibodies in the blood does not contribute to BBB damage. Hence, additional mechanisms may exist, including other pathways for the penetration of antibodies into the central nervous system and the influence of pro-inflammatory cascades [29]. The possibility of indirect effects on the brain is indicated, for example, through changes in the expression of peripheral inflammatory mediators and regulation of homeostasis, which play a critical role in the TNF signaling pathway[6], in ANMDARE patients [29]. A systematic review and meta-analysis published in 2023 demonstrated that the central immune response in ANMDARE is a process that involves multiple cytokine/chemokine-mediated immune cell interactions [30].

CONCLUSION

Therefore, at present, such a disease as ANMDARE exists (although this is not recognized by all psychiatrists; some of whom are trying to reduce all described cases to previous diagnostic units). Moreover, clinical practice and scientific research pose a number of questions to specialists; however, at present, definitive answers are yet to be established.

Most probably, the conditions that are currently called ANMDARE represent a group of diseases with common pathogenetic mechanisms leading to disruption of the normal functioning of NMDA receptors and development of psychopathological symptoms that require differential diagnosics with “primary” mental/psychotic disorders.

The etiological factors that play a role in the development of ANMDARE may vary (tumors including teratomas, viral diseases including COVID-19 and herpes, antiphospholipid syndrome, systemic lupus erythematosus, and “primary” (idiopathic) autoimmune process in relation to NMDA receptors) [31–34].

Furthermore, a characteristic aspect in all of these cases is the prevalence in the clinical presentation of the disease of mental disorders, often acute (peracute) psychotic symptoms. Traditional antipsychotic treatment in these patients leads to pronounced side effects, complicating the already severe somato-neurological status of patients, without improving their mental state. Immunosuppressive therapy is effective in these cases.

However, at the prodromal stage of ANMDARE, when the disease manifestations are limited to affective or subacute hallucinatory–delusional symptoms without catatonic manifestations and signs of confused mental state, standard approaches to the relief of depressive, manic and/or hallucinatory–delusional disorders may be effective. In some of these cases, the titer of antibodies to NMDA receptors remains elevated, although lower than in the acute period of ANMDARE, and its dynamics in an individual patient (as opposed to the average values for a group of patients) can indicate condition severity.

Further studies are required to evaluate the role of antibodies to NMDA receptors in the development of mental disorders.

ADDITIONAL INFORMATION

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[6] TNF is a tumor necrosis factor, a cytokine produced mainly by monocytes and macrophages and regulating intercellular interactions during the immune response.

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