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Энцефалит с антителами к NMDA-рецепторам как курабельная причина острого психоза: возможности диагностики. (Комментарий к статье Е.В. Снедкова «Существует ли анти-NMDA-рецепторный энцефалит?)

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АННОТАЦИЯ

Энцефалит с антителами к NMDA-рецепторам — одна из форм аутоиммунных энцефалитов, который чаще всего дебютирует с острого психоза. С учётом его курабельности и обратимости, энцефалит с антителами к NMDA-рецепторам должен быть включён в список дифференциальной диагностики у всех пациентов с первым психотическим эпизодом. Однако для его диагностики необходимо соблюдать пошаговый алгоритм, принимая во внимание как клинические, так и инструментальные и лабораторные данные. Подтверждение анти-NMDA-рецепторного энцефалита только на основании повышенного уровня антител в крови часто приводит к ложноположительным диагнозам и ошибкам в ведении таких пациентов. В статье освещены особенности диагностики как энцефалита с антителами к NMDA-рецепторам, так и других форм аутоиммунных энцефалитов, которые могут первично дебютировать с острого психоза.

Ключевые слова: *энцефалит с антителами к NMDA-рецепторам, психоз, аутоиммунный энцефалит, тератома*.

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Anti-NMDA receptor encephalitis as a reversible cause of acute psychoses: Diagnostic possibilities. (Comment on the article by E.V. Snedkov “Is anti-NMDA receptor encephalitis real? I. Diagnostic challenges “)

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ABSTRACT

Encephalitis with antibodies to NMDA receptors is a form of autoimmune encephalitis that most often debuts as an acute psychosis. Considering its curability and reversibility, encephalitis with antibodies to NMDA receptors must be included into differential diagnostic list for all the patients suffering first psychotic episode. However, to diagnose it, it is necessary to follow a step-by-step algorithm considering both clinical and instrumental and laboratory data. Confirming anti-NMDA-receptor encephalitis based solely on increased blood antibodies level often leads to false-positive diagnostics and errors in treatment of such patients. In this article, we discuss diagnostic features of encephalitis with antibodies to NMDA receptors, as well as other forms of autoimmune encephalitis that can initially manifest as acute psychoses.

Keywords: encephalitis with antibodies to NMDA receptors, psychosis, autoimmune encephalitis, teratoma.

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BACKGROUND

Anti-NMDA[1] receptor encephalitis (aNMDAre) as a separate nosological form was introduced in 2007 [1]. It was then that antibodies (Abs) to the NR-1 subunit of NMDA receptors were first identified, which were associated with the development of acute psychosis in a patient with ovarian teratoma. Although similar psychotic episodes were described much earlier, Dalmau et al. first described the autoimmune inflammatory nature of this psychopathological condition [1].

Initially, a new case of encephalitis was considered as a particular variant of paraneoplastic neurological syndromes, considering its close association with ovarian teratoma [2]. However, it later turned out that only 30% of all cases are associated with this variant of the "tumor" and that the development of anti-NMDA receptor encephalitis is possible in men, although much less common [3]. Thus, aNMDAre is currently considered as an idiopathic autoimmune process that may be associated with ovarian teratoma; however, the presence of a tumor is not strictly obligate for it [4].

The most common clinical manifestation of NMDA receptor encephalitis is acute psychosis (up to 70%–75% of all cases), which appears after a nonspecific prodromal period [5]. Relatively young age (the most "tropic" age range for NMDA receptor encephalitis is 20–30 years), female sex, and psychotic symptom onset contribute to the fact that most often these patients are initially hospitalized in a psychiatric hospital with a diagnosis of "exacerbation of schizophrenia" [6].

Notably, at the initial stage, the psychotic episode in NMDA receptor encephalitis is practically indistinguishable from that within an endogenous pathology [4]. This is induced by the neurotransmitter imbalance that underlies the development of psychosis in both schizophrenia and the autoimmune process. GluN1 subunit Abs of the glutamatergic receptor in anti-NMDA receptor encephalitis function as partial agonists, stimulating postsynaptic receptors and lengthening the period of opening of ion channels, which can "delay" the period of potentiation and enhance the effect of glutamate [7]. Additionally, potentiation of the glutamatergic NMDA receptor can increase D1 receptor expression and enhance dopaminergic effects [8].

A notable increase in excitatory neurotransmission, and the emerging hyperdopaminergic state, leads to the development of a psychotic episode, which is very similar in its "phenotypic" features to endogenous psychosis.

Although the primary initiating causes of the development of psychosis in schizophrenia and autoimmune encephalitis may be different, the general neurochemical imbalance and common mechanisms of its formation determine substantial difficulties in differentiating psychotic disorders within these two conditions [9]. If we consider acute psychosis as a syndrome that can manifest various types of pathology, autoimmune encephalitis may have strengthened substantially in recent years in the list of conditions that should be included in the list of differential diagnoses in patients with a first psychotic episode [10, 11].

However, like everything new, NMDA receptor encephalitis, which is essentially at the interface of the competencies of two specialties and requires a revision of some previously existing ideas, raises questions, disputes, and discussions.

ANTIBODIESTONMDARECEPTOR: NORM OR PATHOLOGY?

The most common argument used to confirm that NMDA receptor encephalitis can hardly be considered an independent nosological form is the lack of convincing evidence based on the primary pathogenic role of Abs to NMDA receptors. Abs to the GluN1 subunit of the glutamatergic receptor are detected both in patients with long-term psychiatric pathology, without any signs of encephalitis, and in healthy people, although in this case, Abs to other epitopes were most often detected [4, 12]. Various studies have shown higher levels of autoAbs in patients with arterial hypertension and other somatic diseases [13].

In the general population, according to some data, an increase in the level of Abs to NMDA receptors is detected in 20% of cases, depending on age and concomitant diseases, which significantly increases

[1]NMDA: N-methyl-D-aspartic acid

the risk of false-positive diagnoses of anti-NMDA receptor encephalitis if the diagnosis is based only on exceeding the permissible antibody titer in the blood [14].

The availability of laboratory diagnostics and the desire for "novelty" led to the fact that, based on the identification of laboratory markers, previously established diagnoses and treatment regimens were changed in patients, and a diagnosis of autoimmune encephalitis was established where there was no clinical evidence of damage to the central nervous system.

Everywhere there must be a reasonable approach, and aNMDAre has rather strict diagnostic criteria, which include both clinical symptoms reflecting an acute diffuse disorder of the brain and paraclinical confirmation of an organic process [15]. This diagnosis cannot be made outside the clinical presentation of encephalitis.

The modern aNMDAre criteria, developed in 2016 with minor adjustments in 2019, remain relevant today [4].

Diagnostics of probable aNMDAre are possible if all three of the following criteria are met:

1. Rapid onset (<3 months) with at least four of the following six main groups of symptoms:

– Abnormal (mental) behavior or cognitive dysfunction

– Speech disorders (decreased speech fluency and mutism)

– Seizures

– Movement disorders, such as dyskinesia, dystonia, rigidity, and postural disorders (catatonia)

– Decreased level of consciousness

–Autonomic dysfunction or central hypoventilation

2. At least one of the following laboratory results:

– Abnormal electroencephalography (EEG) findings

– Cerebrospinal fluid with pleocytosis or oligoclonal Abs

3. Exclusion of other causes of encephalitis

When identifying an ovarian teratoma, probable aNMDAre can be diagnosed in the case of three of the six clinical symptoms in point 1.

In patients whose clinical and paraclinical data met the diagnostic criteria for aNMDAre and the diagnosis was confirmed by an increased titer of Abs to the NMDA receptor in the cerebrospinal fluid (!), signs of inflammation, corresponding to encephalitis according to autopsy data, were always detected [4, 16].

In Russia, the first wave of interest in autoimmune encephalitis occurred in 2016. Then, in a 28-year-old patient, who died in the psychosomatic department of a multidisciplinary hospital, where she was transferred from a psychiatric hospital with a diagnosis of febrile schizophrenia, malignant neuroleptic syndrome, signs of pro-inflammatory activation were detected at autopsy, making the final diagnosis of autoimmune encephalitis. Although there was no laboratory confirmation, the presence of inflammatory changes in the brain made it possible to conclude about the presence of encephalitis and identify a potentially curable disease as the cause of death, which induced a wide resonance and active discussion of this problem.

It is crucial not to confuse that in patients with an isolated increase in the blood level of Abs, outside the clinical presentation of aNMDAre, it is often not possible to identify any pro-inflammatory markers [17]. However, no one has suggested diagnosing inflammatory brain damage based only on the results of laboratory tests.

The direct pathogenic effect of autoAbs raise many doubts, considering their detectability in various conditions, including in healthy people, and the fact that the risk of developing encephalitis and its severity are not directly related to their quantity.

Apparently, the titer of Abs to NMDA receptors in the blood rather reflects a tendency to more pronounced immune reactions and immune autoaggression, as it is not for nothing that Abs to glutamatergic receptors are combined with other autoAbs (Ab to thyroglobulin, thyroperoxidase, anti-glutamic acid decarboxylase Abs), which can also be present both normally and in pathology [4].

Outside the brain, there are practically no "targets" for Abs to NMDA receptors; under normal conditions, they do not penetrate the blood-brain barrier (BBB). Therefore, their presence in the blood does not trigger a pathological reaction unless special conditions are created [18–20]. One of these "conditions" may be concomitant teratoma [21].

Ovarian teratoma is an embryonic cellular formation containing fragments of various tissues, including nervous tissue. Histochemical studies

revealed that the teratoma expresses a notable number of NMDA receptors. In patients in whom aNMDAre develops against the existing epidermoid ovarian cyst, several autoAbs and signs of a pronounced inflammatory reaction primarily appear in the tumor tissue, and these changes precede changes in the brain substance [22–24]. That is, the teratoma acts as a trigger for "pathogenicity," as autoaggression is primarily directed at it, which triggers the general pathological process.

Thus, teratoma removal serves as a crucial therapeutic strategy because by eliminating the primary source of autoimmunization, the systemic autoimmune process can be better overcome. Teratoma growth appears to be determined by hormonal levels and various gynecological factors. Thus, we monitored two patients whose onset of aNMDAre occurred against intense hormonal stimulation in preparation for in vitro fertilization.

The second most critical "trigger" for developing autoimmune encephalitis is previous infections, primarily caused by herpes simplex virus. A previous study noted that in 27% of patients, wave 2 of deterioration after herpetic encephalitis was associated with an associated autoimmune process, namely, aNMDAre [4, 20]. Apparently, the primary inflammatory process also creates conditions for the "pathogenicity" of Abs to NMDA receptors, as disruption of the integrity of the BBB leads to their entry into the central nervous system, which in turn provokes an immune response due to their foreignness.

In addition to the herpes virus, there has been a close relationship between the development of encephalitis and Abs to NMDA receptors in COVID-19[2], influenza, and various vaccination options, where additional conditions for immune activation are created again[25–27].

Thus, a whole set of causes play a role in aNMDAre development, including innate features of the immune response (according to some data, in patients with autoimmune encephalitis, genetic polymorphism in the group of histocompatibility genes is noted), the presence of Abs to NMDA receptors, and a combination with provoking factors, such as ovarian teratomas or an additional inflammatory process that may contribute to their neuroinvasion. Hence, to avoid false-positive results, it is more informative to use determination of the Ab titer not in the blood but in the cerebrospinal fluid to confirm aNMDAre [16].

However, we consider it not entirely correct to deny the possibility that autoimmune encephalitis may underlie psychosis development in some patients, at least from the standpoint of its curability. Furthermore, 75% of patients with timely initiation of immunosuppressive therapy fully recover, and another 25% of patients have a partial residual defect [4].

Note that in the absence of appropriate treatment, most patients die of progressive autonomic failure. Some cases of "malignant febrile schizophrenia," which has an extremely high mortality rate, fully meet the criteria for aNMDAre. Hence, why not give these patients a chance by considering an alternative, potentially reversible condition as a diagnosis?

We followed up 11 patients with a confirmed aNMDAre diagnosis. Two patients, 26 and 28 years old, died because they were transferred from a psychiatric hospital in an almost terminal stage with severe autonomic failure, and one patient died after cardiac arrest when it was already impossible to do anything [28]. Another three patients were admitted to a psychiatric hospital with an acute psychosis clinic for the first time and stayed there for some time with a primary diagnosis of schizophrenia. They were earlier consulted in a psychiatric hospital with suspected autoimmune encephalitis, when, along with psychotic symptoms, movement disorders and catatonia began to progress. In one case, a generalized convulsive attack developed [29].

Although with further follow-up in all three cases, autonomic failure increased to the point of coma and the need for artificial ventilation, against the immunosuppressive pulse therapy with glucocorticoids along with monoclonal Abs (rituximab); the condition was stabilized; and the patients returned to a full life with absolutely no defects. This may provide further evidence that autoimmune anti-NMDA receptor encephalitis may be a curable cause of acute psychosis.

In all cases presented, the diagnosis was established according to the following criteria: moderate lymphocytic pleocytosis was detected in

[2] COVID-19: Corona virus disease 2019

the cerebrospinal fluid, and the titer of Abs to NMDA receptors was confirmed in the cerebrospinal fluid.

Perhaps another problem in "accepting" the diagnosis of autoimmune encephalitis, aNMDAre, in particular, is not entirely a typical course of the pathological process itself. We are accustomed to the fact that the term "encephalitis" refers to an inflammatory process that leads to the death of nerve cells. This should be confirmed both postmortem and according to intravital studies, for example, by identifying foci of necrosis with diffuse edema according to magnetic resonance imaging (MRI). Immunohistochemical studies of aNMDAre reveal a predominant infiltration of brain tissue by B cells, plasma cells, and CD4 cells, as well as inflammatory activation of microglia [30, 31].

Unlike other forms of encephalitis, in which CD8 T-lymphocytes, which have a direct cytotoxic effect, are most often the main pathogen, CD8 cells are practically not found in aNMDAre, which is apparently due to the relative preservation of neurons [31].

With the conditional viability of nerve cells, the autoimmune process, involving NMDA receptors, leads to severe electrolyte and neurotransmitter disorders, impaired potentiation, and synaptic transmission, which provokes clinical symptoms. The main "clusters" of NMDA receptors in the brain are located in the hippocampus, thalamus, striatum, and other brainstem structures, which induce a typical neuropsychiatric manifestation along with extrapyramidal disorders and autonomic dysfunction [32].

However, emerging functional disorders are not easy to confirm with paraclinical data. Therefore, MRI does not reveal any notable abnormalities in half of the patients, and in the remaining 50% of patients, the nonspecific changes identified were not related to clinical symptoms [4].

According to EEG data, a rather characteristic pattern of changes in the form of an extreme delta brush has been discussed; however, it also reflects gross dysfunctional changes rather than primary neuronal death [33, 34]. Subsequently, when analyzing larger samples of patients, the delta brush was detected in no more than 20% of cases and was not specific for aNMDAre. However, in contrast to MRI data, changes in EEG results can be detected in almost all patients (98.1%), namely, diffuse slowing of the rhythm (40.3%), epileptiform activity (17.7%), extreme delta brush (16.1%), polymorphic delta rhythm (9.7%), focal slowing of activity (8.1%), and diffuse beta activity (6.5%) [4, 35, 36]. Apparently, such a high frequency of EEG changes is due to the fact that in the absence of primary damage to the structure, deviations in neurophysiological parameters are more valuable for confirming aNMDAre.

Thus, the pathological process features within aNMDAre do not lead to focal brain damage but to gross diffuse disorganization, which gives the specificity of the clinical presentation in the form of psychoses, episyndrome, cognitive dysfunction, and behavioral disorders without classical "neurological" symptoms.

aNMDAre is not the only form that can manifest as an acute psychotic episode at its onset and cause difficulties in differential diagnosis between primary endogenous pathology and autoimmune encephalitis. Presently, >300 potential Abs have been described that have tropism for receptors and ion channels under certain conditions, and can trigger similar clinical symptoms. However, the availability of their definition throughout the world is quite low, and there is no clear specificity for some very precise forms.

In 2020, an international consensus proposed a general definition of autoimmune psychosis, which does not imply the definition of any particular nosological form. This included both cases of psychotic disorders during paraneoplastic processes and idiopathic forms of autoimmune encephalitis [37].

Suspicion of possible autoimmune genesis should arise in the presence of psychotic symptoms with an acute onset and rapid progression (within <3 months) along with at least one of the following:

– Presence of a tumor or cancer

– Movement disorders (catatonia or dyskinesia)

– Negative "response" to neuroleptics and possible diagnosis of neuroleptic malignant syndrome (rigidity, increased creatine phosphokinase activity, hyperthermia)

– Cognitive dysfunction

– Impaired consciousness

– Seizures

– Clinically notable autonomic dysfunction (fluctuations in blood pressure, body temperature, heart rate)

If the clinical criteria are met (clinically possible autoimmune psychosis), a mandatory additional examination is performed, namely, MRI, EEG, lumbar puncture (general analysis of the cerebrospinal fluid and the level of oligoclonal Abs), and Abs for autoimmune encephalitis in the blood and cerebrospinal fluid (according to availability).

The diagnosis of probable autoimmune psychosis is established when the clinical presentation is combined with the following parameters:

At least one of the following:

– Pleocytosis in the cerebrospinal fluid >5 cells in 1 μl

– Bilateral changes in the temporal lobe according to MRI, hyperintense in flair

Or at least two of the following:

– EEG changes (sharp waves/slowing of activity/ focal changes/extreme delta brush, etc.)

– Oligoclonal Abs in the cerebrospinal fluid or increased immunoglobulin G index

– Increased levels of Abs in the blood

A confirmed diagnosis can only be established by identifying specific Abs in the cerebrospinal fluid.

Although final confirmation by the level of Ab is not always available, such a step-by-step algorithm will allow psychiatrists to be more alert regarding the possible autoimmune nature of the patient's condition and will enable them to avoid false-positive diagnoses outside the clinical context.

CONCLUSION

Thus, considering clinical, laboratory, and immunohistochemical studies, anti-NMDA receptor encephalitis can be considered a separate nosological form and an alternative diagnosis in the differential diagnosis of patients with the first psychotic episode.

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