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Autoimmune Anti-NMDA Receptor Encephalitis

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Encephalitis with antibodies to glutamate NMDA receptors (anti-NMDA receptor encephalitis, ANRE) is a relatively common form of autoimmune encephalitis. Clinical symptoms at onset are similar to the symptoms of exacerbation of schizophrenia, such that these patients are often hospitalized in psychiatric institutions. Considering the high lethality of this condition, and also its potential curability, detection of ANRE is an important clinical task. We present here the first laboratory confirmed case of ANRE in the Russian literature. Difficulties preventing the prompt resolution of the condition are presented, along with criteria for its diagnosis and a treatment algorithm.

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

Recent advances in neuroimmunology have led to the identification of a group of new neurological diseases, i.e., autoimmune forms of encephalitis (encephalopathies). Due to autoimmune attacks directed against various antigenic targets in the CNS (primarily glutamate, dopamine, GABA receptors, and also calcium channels), they are characterized by subacute onset with fast progression, or a fluctuating course with alternation of exacerbations and remissions, multifocal brain lesions with bizarre combinations of symptoms of stimulation and loss of functions, and nonspecific and minimal findings from neuroimaging and routine investigation of the cerebrospinal fluid (CSF). When disease is severe, patients are often in a critical state, though prompt diagnosis and appropriate treatment, even in severe cases, can lead to complete recovery. Unfortunately, such cases are often interpreted by practical physicians as an unusual form of mental pathology, an infectious disease, or multiple sclerosis, such that the opportunity for radical intervention and prevention of an unfavorable outcome is missed.

One of the main members of this group of diseases is autoimmune encephalitis with anti-NMDA glutamate receptor antibodies (anti-NMDA receptor encephalitis, ANRE). This was first described by Vitaliani et al. [1] in 2005 in a patient with an ovarian teratoma with acutely developing mental disorders, severe amnesia, and episodes of confusion, disorientation, and central hypoventilation. It was only after two years that an antigen operating as a target for autoimmune attack and inducing this symptomatology was identified. This was the GluN1 subunit of the NMDA receptor, the highest density of which is found in hippocampal neurons [2]. Antibodies to NMDA receptors have high diagnostic specificity; their pathogenicity has been demonstrated in neuron cultures and in vivo.

Adequate assessment of the incidence of ANRE is difficult, though periodic reports of new clinical cases suggest that it is much more common than previously suggested. Thus, during the three years after the first publication in 2005 and detection of antigens in the NMDA receptor subunit in 2007, 417 cases of ANRE were published [3], which was greater than the incidence of cases of limbic encephalitis (200 cases over a 13-year observation period [4] and 500 over a six-year period [5]). Until recently, however, the limbic type was regarded as the most common form of autoimmune encephalitis. Retrospective analysis showed that ANRE accounted for 1% of cases of encephalitis [6], while in the UK the incidence of this disease reached 4% of all cases of inflammatory brain disease [7]. The disease mainly affects young people (95% of patients are below 45 years of age and 37% are younger than 18 years).

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Analysis of the literature showed that no cases of this disease have as yet been described in Russia. We present a clinical observation with laboratory confirmation of autoimmune ANRE.

Case history. The patient, female, age 28 years, was brought to a psychiatric hospital by ambulance. The duty psychiatrist diagnosed acute polymorphic disorder with symptoms of schizophrenia. History: no inherited burden, higher education, employed as economist in a bank.

The medical records show that during the 10 days prior to hospitalization, the patient experienced elevated anxiety, accompanied by drowsiness (she was sleeping about 15 hours/day). The patient complained of general exhaustion, malaise, and weakness, associated with the fact that she had not slept "for almost a week." She then realized that she was hearing music and voices, which prevented her from going to sleep. The patient became aroused and aggressive, did not let her relatives go home, shouted things out, and tried to hit them. Family members reported that she spoke of voices and gave the impression of a person subject to some kind of influence. She shouted "What do I have to do?," switched appliances on and off, started but did not finish everyday tasks (washing dishes, cleaning floors, dusting), paced around the apartment grasping new objects, repeating "I must, I must..." Periodically she would hold her head and cry out "It's scary, it's scary...," "Get it out of my head...," "Hold me, hold me, it's me in my head...," "Why are you taking my energy?..." She was oriented in space and self and recognized relatives. She periodically cried out, blamed her mother, friend, and sister, and then, conversely, said that they were clever, kind, and loving, and wrung her hands, held her head, and was aggressive, with the result that the paramedics were formed to hospitalize her in the psychiatric institution.

On admission, the patient displayed marked psychomotor arousal. Formally, the patient was conscious but made no productive contact; facial expression was bewildered, "spellbound." Then she said she was in hospital in Moscow, next she claimed she was in Finland. She called herself by another name, said she was 50 years old, left many questions unanswered, giggled, periodically became enraged, and cried "Stop." She felt as though she was under some influence, constantly hearing music and "something else" in her head. She often said individual words with no connected meaning. She was negative and resisted examination. Overall, the patient appeared drowsy, but became aroused on persistent questioning, actively waving her hands and swearing angrily. From admission she was treated with risperidone (9 mg/day) and phenazepam (2 mg/day).

On hospital day 4, the patient was noted to have disorganized thought and behavior, episodes of arousal and aggression; she was voluble, though most of her words and sentences made no sense; she refused to eat or drink, with the result that haloperidol (4 mg/day) was added to treatment. On the next day, there were increases in drowsiness and inhibition; she did not get out of bed. Responses consisted of single words with no relationship to the question. She could only eat and drink when forced. Leukocytosis ($12.3 \cdot 10^9$ per liter) led to examination by a therapist and suspicion of exacerbation of chronic bronchitis, so ceftriaxone (2.0 i.m. / day) was added to treatment. Instability of BP was noted on the same day, with a tendency to hypertension to 160/100 mmHg, tachycardia to 120 bpm, normal body temperature, and absence of focal neurological symptomatology.

The next day, the patient could not be contacted, did not follow instructions; speech was blurred, she was constantly muttering something, and made stereotyped hand movements; attempts to feed met with active resistance. Aminazine (2.0 i.m.) was prescribed. Consultation with a diagnosis of "catatonic stupor with refusal to eat" led to transfer to a psychiatric hospital with an intensive treatment unit.

On admission, the face was masklike, gaze was fixed, and was directed forward. When addressed, gaze was not fixed, expressions of fear and suffering appeared on her face, and the patient groaned continuously. She did not respond to questions or follow instructions. Passive negativism was apparent: attempts to examine her led to her closing her eyes tightly. Oral dyskinesia was noted for the first time, with stereotypical movement of the lower jaw and pressing the lips together. Dyskinesia of the feet and hands also occurred, with periodic dystonic trunk movements.

On day 18 from onset of illness, the patient developed a generalized convulsive seizure, after which there was no spontaneous respiration and blood pressure and pulse could not be determined. Resuscitation led to reinitiation of cardiac activity and the patient was intubated and transferred to mechanical ventilation. Hyperthermia, to 38.8°C, was noted for the first time. Treatment: dopamine solution via automatic infusion, ceftriaxone 4 mg/day i.v., gentamicin 240 mg/day i.v., biperiden solution 0.5%, 1 ml by i.v. infusion, and physiological saline, 1200 ml/day.

Multidisciplinary consultation the next day, involving an anesthetist, psychiatrist, neurologist, neurosurgeon, and an infectious diseases specialist led, given the patient's severe condition, to transfer to the intensive care department of a general hospital with a diagnosis of "Space-occupying lesion of the left hemisphere of the brain. Coma of unknown origin. Condition following convulsive seizure and clinical death with resuscitation. Mechanical ventilation. Acute psychiatric disorder. Neuroleptic syndrome." On admission to the intensive care unit: condition severe, coma 1 (on the background of medication-induced sedation), pupils symmetrical, eyeballs fixed in the midline, oromandibular dyskinesia with protruding tongue, spontaneous involuntary movements of the upper limbs, tendon reflexes decreased without clear differences between sides, bilateral Babinski reflex. No meningeal syndrome. Clinical blood tests: leukocytosis to $17.3 \cdot 10^9$ per liter, elevated concentrations of urea, glucose, transaminases, and creatine phosphokinase to 1889 U/liter. CT with contrast: no focal brain lesion seen. Treatment with carbamazepine (200 mg twice daily) was initiated.

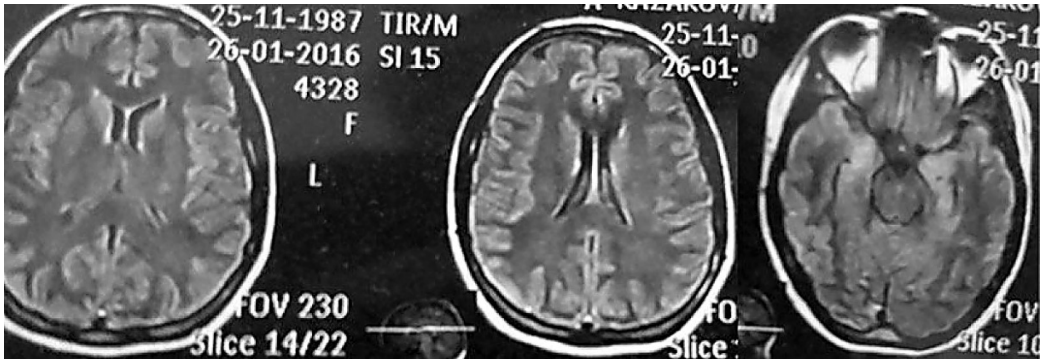

Fig. 1. MRI image, FLAIR regime. Increased signal intensity from the mediobasal parts of the temporal cortex.

On the following day, there was no significant change in state: hyperthermia to 38.6°C, mechanical ventilation, medicinal sedation (thiopental sodium). Lumbar puncture was performed. CSF showed pleocytosis (112/3, lymphocytes 63%, neutrophils 37%) with normal protein and glucose levels. Considering the onset of illness with cognitive and psychotic impairments, with addition of motor impairment in the form of oromandibular dyskinesia and dyskinesia in the limbs, epileptic seizure, and moderate lymphocytic pleocytosis in the CSF, it was suggested that the patient had autoimmune encephalitis (possibly associated with anti-NMDA receptor antibodies) or viral (possibly herpes) encephalitis. Investigation of the CSF by PCR for herpes viruses was ordered, along with blood tests for anti-NMDA receptor antibodies, and an MRI brain scan. Treatment with methylprednisolone (1000 mg/day i.v.) and acyclovir (2 g/day until PCR results were available) was started.

The MRI brain scan showed increased signal intensity in the DWI, T2, and FLAIR modes from the mediobasal temporal areas and the lower parts of the caudate nuclei (Fig. 1).

Over the next three days, the patient's condition remained severe. Hyperthermia to 38.6°C persisted. PCR results for herpesvirus were negative. Acyclovir infusion was terminated. Ultrasound scan of the pelvic organs showed a mature teratoma of the right ovary. On day 25 of illness, a positive blood test for antibodies to NMDA receptors was obtained (total titer of IgG, A, M = 1:160, compared with a normal level of <1:10), giving a diagnosis of ANRE on the background of teratoma of the right ovary. Administration of methylprednisolone 1 g/day was continued for seven days, after which escalation of immunosuppressive therapy was considered. The patient's condition deteriorated sharply the next day; the level of suppression of consciousness increased, body temperature reached 40°C, systemic pressure dropped to 60/40 mmHg, and vasopressor support was required. The patient died on day 27 from onset of illness on the background of acute cardiac failure.

The literature [8, 9] contains data on more than 500 cases of ANRE, analysis of which identifies the characteristic clinical symptoms of both the acute and recovery phases of illness. A prodromal period was noted in 70% of cases, with general weakness, headache, dyspeptic symptoms and signs (nausea, vomiting, diarrhea), fever, and in some cases symptoms of infection of the upper respiratory tract.

Severe psychotic impairments generally appear over the first two weeks, often leading to admission to psychiatric hospitals with suspected onset of schizophrenia. The most frequent symptoms of mental debut are anxiety, fear, insomnia, a manic state, delusions (paranoid syndrome with motives for developing hyperreligiosity has been described), and hallucinations of different modalities [10]. Most patients show memory disorders, along with speech disorders with the development of echolalia and rapid conversion to mutism [11].

Increasing cognitive, psychotic, and behavioral symptoms are joined in almost 90% of cases by extrapyramidal symptoms – orofacial dyskinesia, frequently with characteristic tongue movements (of the "snake tongue" type), chorea, or stereotypy, more rarely dystonia and rigidity of the limbs, and possible development of ocular crises and opisthotonus. Considering the onset of disease with psychotic symptomatology, almost 100% of cases are given neuroleptics, often leading to erroneous assessment that there is a link between the motor manifestations and catatonia with complications of neuroleptic therapy.

As the disease develops, the patient ceases to respond to external stimuli and episodes of psychomotor arousal can be replaced by catatonia. Increased body temperature combined with catatonia may lead to the suspicion of febrile schizophrenia or malignant neuroleptic syndrome, which hinders the diagnostic search and delays establishment of the diagnosis. In fact, neuroleptics can worsen the patient's condition, promoting faster progression of illness, though extrapyramidal symptomatology also develops without prescription of these agents.

Apart from hyperthermia, patients with ANRE can also develop other autonomic disorders: tachycardia and bradycardia, arterial hypertension or hypotension, hypersalivation, urinary incontinence, etc. Typical sharp oscillations

occur, from tachy- to bradycardia, from hypo- to hypertension, and from hyper- to hypothermia (autonomic instability). Impairments to respiratory and cardiac activity may require constant infusion of vasotonics and transfer of the patient to mechanical ventilation [10]. Respiratory failure mostly appears when consciousness decreases to the level of coma, though respiratory impairments may also develop with relatively normal levels of consciousness.

The phenomenon of dissociative anesthesia is commonly seen, this being more typical for the actions of NMDA receptor antagonists (ketamine, phencyclidine); there is a complete absence of contact or responses to pain stimuli, the patient is formally conscious – lying with the eyes open and the gaze fixed at a single point. Epileptic seizures, developing in almost 85% of patients, often go unnoticed because of concomitant extrapyramidal impairments, psychomotor arousal, or the need to maintain medicinal sedation. Seizures may be generalized or focal, and are often accompanied by worsening of autonomic impairments. In some cases, these are first seen on background of recovery from medicinal sedation [11].

The literature contains descriptions of "mild" (monosymptomatic) ANRE with prolonged dominance by one of the symptoms of the condition. Thus, cases with isolated psychotic symptomatology, epileptic seizures, dystonia, or other neurological symptoms have been described, though this occurs in less than 5% of patients. Seizures, like extrapyramidal symptoms at onset, develop more often in children. The monosymptomatic nature of the conditions is generally temporary and the disease goes on to acquire the developing clinical picture. By weeks 3–4, almost 90% of patients form a more or less typical picture, including most of the following main groups of syndromes: cognitive, behavioral, extrapyramidal disturbances, autonomic instability, and hypoventilation, epileptic seizures, cerebellar, and pyramidal impairments. For example, Dalmau et al. [11] described the development of isolated manic syndrome in a 19-year-old male, who developed memory impairment and signs of orofacial dyskinesia over three weeks.

Neuroimaging methods do not generally identify any specific changes, though MRI scans in the T2, FLAIR, or DWI regimes sometimes reveal hyperintense signals from the hippocampus and medial sections of the temporal lobes (this pattern may be reminiscent of limbic encephalopathy), the cortical areas, subcortical or brainstem structures, or, more rarely, the spinal cord [2]. In most cases, these changes are moderate and can be transient or stable, though they generally do not correlate with the clinical pattern or severity of the condition [10, 12]. Previous studies identified moderate cortical atrophy in patients with refractory epileptic seizures, poor recovery, or with lethal outcomes, though on the background of more aggressive immunoactive therapy, cases with poor recovery have become rarer and there are virtually no data on secondary atrophic changes in the cortex [2, 13]. Studies using positron emission or single-photon emission computerized tomography have demonstrated variable changes in the cortical and subcortical parts of the brain, though these are sometimes absent at the early stages of disease [13–16].

EEG data are variable and depend on the stage of disease. Periodic sharp- or peak-wave activity can be seen, which on rapid progression of cognitive, behavioral, and motor impairments sometimes lead to erroneous diagnoses of Creutzfeldt–Jakob disease [11]. However, in most cases the EEG shows show nonspecific changes in the form of disorganization and slowing of activity [17].

In 80% of patients, the CSF shows moderate lymphocyte pleocytosis and slightly elevated protein; 60% show oligoclonal antibodies [11]. Changes in the CSF may persist throughout the whole period of illness and the recovery period, the extent not correlating with the severity of the patient's condition and may be independent of treatment efficacy.

The most specific diagnostic criterion is an increase in the titer of anti-NMDA receptor antibodies in the blood and CSF [3, 11, 18]. The specificity of this method of diagnosis is about 80%, which leaves room for false positive results. In order to avoid overdiagnosis, the clinician should always evaluate laboratory data in the clinical context. In addition, there is value in investigating antibodies in both the blood and the CSF and repeating these over time. Determination of CSF antibody levels has no significant advantage over blood assays, though cases of so-called seronegative encephalitis have been described in which blood tests were negative and CSF tests were positive. False positive results in blood are seen in the acute period of illness and after immunosuppressive therapy (particularly plasmapheresis and i.v. administration of immunoglobulin). In these cases, antibody can be detected only in the CSF [6, 17], though the reverse dissociation can also occur [19].

Considering that ANRE was initially described in women with ovarian teratomas, this form of CNS lesion was for some time regarded as an exclusively paraneoplastic process. As more new cases were described, and because of the introduction of testing for anti-NMDA receptor antibodies into clinical practice as a routine screening test, it came to be understood that the process was not infrequently idiopathic. Idiopathic ANRE was mostly encountered in children and adolescents; however, as age increases, the proportion of paraneoplastic cases increases.

This type of encephalitis is most commonly encountered in combination with ovarian teratoma, which explains the high morbidity of the disease in women (with a 4:1 ratio) [11]. Gender-related differences in morbidity are less significant before 12 years of age and over 45 years of age. ANRE can also develop of the background of other tumors (no more than 2% of cases). Cases of its development in lymphoma, neuroblastoma, and small cell lung cancer have been described [10, 20, 21]. However, while a causal relationship between two pathological processes is beyond doubt for teratoma (studies of teratoma tissue identified

TABLE 1. Diagnostic Criteria for ANRE

Confidence in diagnosis	Diagnostic signs
Probable	1. Rapid development (less than 3 months) and at least four of the following six groups of symptoms:* behavioral and cognitive impairments, speech impairments (dysarthria, logopenia, mutism), epileptic seizures, extrapyramidal impairments (dyskinesias, rigidity, pathological postures, etc.), decreased consciousness, autonomic dysfunction or hypoventilation
	2. At least one of the following paraclinical signs: changes in EEG (focal or diffuse slow or disorganized activity, epileptic activity, bursts of δ-waves), changes in CSF (pleocytosis or oligoclonal antibodies)
	3. Exclusion of other diseases
Confident	1. Presence of at least one of the six groups of symptoms
	2. Antibodies (IgG) to GluN1 NMDA receptors**
	3. Exclusion of other diseases

* If teratoma is present, three of the six groups of symptoms are sufficient.
** Tests for antibodies should be performed on CSF as well as blood

NMDA receptors), the nature of the connection for combinations of encephalitis with other tumors requires further study. The frequency of tumor detection depends on age and gender: it is 0–5% in children, 58% in women aged over 18 years (usually ovarian teratoma), and 23% in patients aged over 45 years (usually carcinoma).

Identification of teratoma in patients with ANRE has both diagnostic and therapeutic value: removal of the tumor is the most important condition for resolving the pathological process. Despite the fact that teratoma itself may not be malignant, its removal at both the subacute and recovery periods may lead to significant clinical improvement and decreases in the risk of recurrence [10, 22]. Tumor-associated encephalitis is characterized by a more severe course and is often accompanied by profound depression of consciousness, though there is a better response to immunotropic therapy [10, 11, 17]. Thus, all female patients with suspected autoimmune encephalitis should undergo screening for teratoma (MRI, CT, ultrasound scan of the pelvic organs). Assay of currently available oncomarkers (CA125, β-HCG, α-fetoprotein, or testosterone) may give negative results in some patients even when a tumor is detected, so the diagnostic value of these tests remains uncertain.

Considering that at the onset of disease, it is difficult to differentiate ANRE from viral and other infectious processes, most of the cases described have been screened for pathogens. Thus, apart from anti-NMDA receptor antibodies, patients showed positive serological reactions for mycoplasmas (more often in children); there are publications describing the combination with infections with herpes simplex virus and influenza [23, 24]. Detection of concomitant inflammatory processes is entirely explicable given the involvement of immune mechanisms in the development of autoimmune encephalitis: infectious antigens may trigger an autoimmune reaction. For this reason, ANRE can evidently develop after vaccination. A particularly close link has been seen between ANRE and herpes infection. Testing for antibodies to NMDA receptors is indicated in recurrent symptomatology (for example, detection of choreoathetosis or mental disorders) some weeks after herpes encephalitis. Some patients with antibodies to NMDA receptors show other autoantibodies – markers of "competing" autoimmune diseases (antinuclear, antibodies against thyroid peroxidase and thyroglobulin), which emphasizes the importance of assessing serological data in the clinical context [17, 25].

With prompt initiation of therapy, about 70–75% of patients with ANRE show complete or almost complete recovery. The remaining cases form profound neurological, including cognitive, deficits or experience lethal outcomes. The frequency of death reaches 25% in some series [11].

Treatment is based on various methods of immunosuppressive therapy, along with detection and removal of teratoma. First-line agents are corticosteroids (generally pulse therapy with methylprednisolone 1 g/day), i.v. immunoglobulin, and/or plasmapheresis. As the time taken for assay of anti-NMDA receptor antibodies is about 10 days, the rate of progression and the risk of lethal outcome requires a decision to be taken about performing an immunotropic therapy trial as soon as the disease is suspected (for example, corticosteroid pulse therapy or i.v. immunoglobulin, 0.4 g/kg/day for five days). After obtaining positive analysis results for anti-NMDA receptor antibody and, considering the results of the treatment trial, the question of prescribing second-line therapy arises (monoclonal antibody rituximab or the cytostatic agent cyclophosphamide).

In the combination with encephalitis with ovarian teratoma, the efficacy of these treatment methods reaches 80%, compared with 48% in the absence of teratoma. Thus, one view [7, 10, 11, 26–28] is that in severe cases, when no tumor is detected, first-line drugs should be prescribed in combination of second-line immunosuppressants (rituxumab, cyclophosphamide).

Removal of teratoma is an important element of treatment, and in some cases improvement is achieved literally within hours of surgery. However, surgery cannot be performed in some patients because of the severity of the condition. Data from a systematic review [29] show that teratoma is usually removed between 39 and 72 days depending on the age and type of tumor. The optimum (recommended) time for removal is 4–8 weeks from the onset of the clinical picture.

Evidence-based recommendations for the management of patients with ANRE in resuscitation departments have not been developed. Given that the symptoms of encephalitis are largely reminiscent of the signs of overdosage with NMDA receptor antagonists, use of substances with analogous actions (for example, ketamine) should be avoided. Splinter and Eipe [30] described the development of arterial hypotension on administration of propofol, though repeat administration after several weeks did not produce adverse events and tolerance was good.

Recovery of patients after ANRE is slow and takes from several months to 2–3 years. Impulsivity, disinhibition, inappropriate behavior, hyperphagia, hypersexuality, hypersomnia, and in some cases Klüver–Bucy syndrome or Kleine–Levin syndrome, require prolonged rehabilitation. About 20–25% of cases show recurrences with different intervals between exacerbations and variable residual symptomatology in the "cold" periods [7, 11]. Recovery may also occur spontaneously, though, according to existing data [13], survival and the prognosis for recovery and the risk of recurrence depend on the timing and activity of treatment,

In the present observation, the disease produced classical symptoms: after a one-week prodromal period, the patient developed acute arousal, confusion, delusions, and hallucinations, with subsequent addition of motor impairments (including oromandibular dyskinesia and stereotypy), catatonia, epileptic seizures, and profound autonomic disorders (hypoventilation, hyperthermia, oscillations of arterial blood pressure, tachycardia).

The diagnosis was also confirmed by paraclinical investigation data – moderate lymphocytic pleocytosis, increased signal from the mediobasal parts of the temporal lobes on MRI scans, and ultrasound scan detection of a mature teratoma of the right ovary. A confident diagnosis of ANRE was made on the basis of finding a high titer of anti-NMDA receptor antibodies in the blood (1:160).

Of the characteristics of this observation, note should be taken of the rapid rate of progression (less than one month from the prodromal phase to death), the severe autonomic instability, on the background of which there was an episode of clinical death after a convulsive seizure, as well as the absence of any clinical effect with methylprednisolone, which may be connected with the relatively late prescription (day 21 from the onset of the prodromal phase).

In conclusion, it should be emphasized that timely diagnosis of ANRE requires doctors of all specialties (particularly neurologists, psychiatrists, gynecologists, and resuscitation specialists) who might encounter this highly dramatic but treatable disease to be on the alert. ANRE should be suspected in all persons of less than 50 years of age, especially in children and adolescents with rapidly developing psychotic, cognitive, and behavioral impairments, with early addition of extrapyramidal disorders (dyskinesia, stereotypy, rigidity), catatonia, epileptic seizures, and autonomic symptoms (hyperthermia, hypoventilation, hypertension, arrhythmia, etc.). Signs confirming the diagnosis include lymphocytic pleocytosis in the CSF with the presence of oligoclonal antibodies and possible moderate increases in protein levels; slow-wave disorganized EEG activity, and MRI changes consisting of hyperintense signals in the FLAIR, T2, and DWI regimes with possible accumulation of contrast medium. High levels of pleocytosis and significant increases in CSF protein levels, along with profound changes on MRI scans (especially with formation of areas of necrosis or the presence of mass effects) exclude the diagnosis of ANRE and necessitate a search for alternative causes (particularly viral encephalitis). Criteria for the diagnosis of encephalitis were published recently (see Table 1) [31]. All patients with suspected autoimmune encephalitis should be investigated for blood and CSF anti-NMDA receptor antibodies and undergo screening for ovarian teratoma. Even if no tumor has been detected at the moment of onset of encephalitis, screening should be repeated for at least two years.

The authors have no conflicts of interests.

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