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Anti-NMDA receptor encephalitis – the narrative review of literature with particular regard to pediatric population

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Summary

In recent years, the frequency of diagnosing autoimmune encephalitis has increased significantly, both in the population of adults and children and adolescents. This fact is undoubtedly related to the dynamic development of new diagnostic methods, as well as the progress of medical knowledge. A particular type of this condition is anti-NMDA receptor encephalitis. Due to the presence of psychiatric symptoms in this disease, psychiatrists are often the first specialists who treat a patient with the above diagnosis. Differential diagnosis is extremely difficult and primarily based on the history and presence of typical clinical symptoms. Therefore, based on a narrative review of the literature on the subject searched by the PubMed, EMBASE, and Cochrane library databases from 2007–2021 with the keywords "anti-NMDAR encephalitis", "children", and "adolescents", the author described the characteristic course of the disease, diagnostic methods used to confirm the diagnosis, and presents current treatment guidelines. Due to high prevalence, anti-NMDA receptor encephalitis is a diagnosis that should be considered in the differential diagnosis in everyday psychiatric practice.

Key words: children and adolescents, anti-NMDAR encephalitis

Introduction

Anti-NMDA (anti-N-methyl-D-aspartate) receptor encephalitis is an autoimmune disease that was first described by Dalmau et al. in 2007 [1]. The initial descriptions concerned women with ovarian neoplasms (most often teratomas), followed by also men with testicular neoplasms; therefore, it was categorized as a paraneoplastic syndrome. The presence of teratomas is much more common in women, especially of African descent [2]. Other tumors such as neuroblastoma and Hodgkin's lymphoma are much less frequently present [2]. In subsequent studies, it turned out that in younger patients (< 12 years old) and in men, neoplastic changes are not as common. It is known now that in children under the age of six, neoplastic changes are most often not present

[2, 3]. Due to the above data, the diagnosis is now being withdrawn from the group of paraneoplastic syndromes.

As it is a relatively new type of encephalitis, the aim of the article was to present the characteristic course of this disease, discuss diagnostic tests to confirm the diagnosis and present current treatment guidelines. For this purpose, a narrative review of the literature on the subject searched by the PubMed, EMBASE, and Cochrane library databases from 2007-2021 with the keywords "anti-NMDAR encephalitis", "children", and "adolescents" was performed.

Epidemiology

Currently, the number of epidemiological studies is too small to determine the exact incidence of anti-NMDAR encephalitis. However, previous studies show that this disease is more common than paraneoplastic syndromes [2].

In the Granerod et al. study [4], this diagnosis was made in 4% of the group of 203 patients with encephalitis; thus, it came second after ADEM (acute disseminated encephalomyelitis, which was diagnosed in 11% of patients) in the category of autoimmune encephalitis. In other studies, the diagnosis of anti-NMDAR encephalitis was made more often than the diagnosis of paraneoplastic syndrome, and also more frequently than the diagnosis of any viral neuroinfection other than HSV (herpes simplex virus) neuroinfection (which was diagnosed in 19% of patients) [4-6].

Although hypotheses regarding the potential relationship between the occurrence of disease symptoms and a specific viral infection have been analyzed, no such relationship has been documented so far [7]. There is a concept of the influence of HSV infection on the activation of autoimmune processes – however, due to the small percentage of patients participating in the study [8], the above thesis requires verification.

The disease most often occurs in patients aged 12-29 years [5], predominantly female. Descriptions of patients < 12 years of age and men are much less frequent, but now there are data confirming the diagnosis in increasingly younger patients: in the study of Wandinger et al. [9], the youngest patient treated so far was 23 months old, and in the Kayser and Dalmau [8] study the age range was defined as 2 months – 85 years [see also 3]. The authors emphasize a different course of the disease in the pediatric population, with a prevalence of neurological symptoms over psychiatric ones [8].

Pathophysiology

The NMDA receptor is one of the glutamatergic receptors. It is a tetrameric complex consisting of the following subunits: the fixed glycine-binding subunit (NR1) and various combinations of glutamate-binding subunits (NR2 or NR3) depending on the location of the receptor, its function and CNS maturity. Glutamate is one of the major excitatory neurotransmitters in the central nervous system.

The proper activity of NMDA receptors is related to the processes of regulating the work of synaptic connections and the maturation of neurons; it plays an important role in processes related to brain plasticity, knowledge acquisition, memory functions, as well as the perception of sensory stimuli such as visual and auditory. Excessive activity of these receptors lowers the seizure threshold, which can lead to the onset of epileptic attacks. It is also observed in patients with dementia or after a stroke. Low activity or blocking of the receptor, on the other hand, has anticonvulsant but also propsychotic effects [10].

In healthy people and animals, pharmacological reduction of NMDA receptor activity with antagonists such as ketamine or phencyclidine (PCP) causes disturbances in working memory, perception, executive function disorders, and psychotic symptoms. The symptoms depend on the dose of psychoactive substances:

- small doses usually cause illusions, paranoid thoughts, but no memory or executive function disorders are observed;
- medium doses cause more intense psychotic symptoms with agitation, aggression, memory disorders, and decreased reactivity to pain stimuli;
- high doses are associated with the occurrence of coma, catatonic symptoms, and autonomic disorders [5].

The pathomechanism in autoimmune encephalitis with anti-NMDAR antibodies concerns the binding of specific antibodies to epitopes located in the extracellular part of the NR1 subunit of the NMDA receptor. This causes a reversible reduction of receptors on the surface of the neuron [9], which negatively affects the synaptic plasticity and the functioning of neural networks, without a significant reduction in the number of neurons. In the acute phase, activation of the autoinflammatory process associated with the activation of B lymphocytes, plasma cells and microglia is observed [11].

Symptoms

The course of the disease can be divided into several consecutive stages: prodromal, psychotic, neurological (with the possibility of seizures), catatonic or associated with alterations in consciousness, and the stage of recovery. In over 70% of patients, the first symptoms are preceded by flu-like symptoms such as headache, fever, nausea-diarrhea-vomiting, symptoms of upper respiratory tract infections and weakness [7].

About two weeks after the onset of prodromal symptoms, the first symptoms related to the inhibition of the NMDA receptor are present. The most common are: bizarre behavior, confusion, paranoid thoughts, grandiose delusions, hyperreligiosity, visual and auditory hallucinations, anxiety symptoms, insomnia, manic symptoms, and catatonia. For this reason, patients often visit psychiatrists and receive antipsychotic treatment [9]. Short-term memory deficits are also often described, although they may be a symptom masked by speech disturbances or psychotic symptoms [2]. Symptoms such as social withdrawal, stereotypical behavior, and rapid deterioration of linguistic

functions (ranging from verbal reduction, echolalia with echopraxia to mutism) are described less frequently.

In young children, behavioral changes can be difficult to assess as the picture may not be as typical as in older patients. Psychotic symptoms are less frequently described, and more often outbursts of anger, hyperactivity or irritability. Hypersexual behavior, aggression, anxiety symptoms and insomnia are also observed in children, often requiring pharmacological sedation. Often, in young children, the diagnosis is based on neurological symptoms that may dominate the picture, such as seizures or status epilepticus, dystonia, speech disorders, and mutism [2].

In the next phase of the disease, neurological symptoms and autonomic dysfunction appear. The neurological symptoms are mainly extrapyramidal symptoms such as: stiffness, dystonia [7], dyskinesias typically occurring in the orofacial region consisting of grimaces, chewing/biting movements, forced opening and closing of the mouth with gum and tongue injuries and tooth fractures, other dyskinesias [10], choreoathetosis, oculogyric crises, opisthotonus, and akinesia [2]. The disease may be accompanied by epileptic seizures, especially in the pediatric population. It is believed that in this age group they occur much more often than in viral encephalitis – even up to 80.7% [12]. The most common are focal seizures, less often generalized tonic-clonic seizures. Status epilepticus is also relatively common in this age group – up to 43.5% [12].

Of the autonomic symptoms, the most commonly observed are hypoventilation, hyperthermia, arrhythmias (bradycardia, pauses, tachycardia), fluctuations in blood pressure (hypertension, hypotension), hypersalivation, urination disorders, and erectile dysfunction. Fluctuations in intracranial pressure have been observed in a few patients. Hypoventilation often requires artificial ventilation for up to several months [2]. Due to autonomic instability, patients often require intensive care units [9].

In the following phase, catatonia or various disturbances of consciousness are usually observed. A fluctuation of symptoms with periods of alternating agitation/akinesia is typical. During the period of agitation, a paradoxical reaction to stimuli (e.g., no reaction to pain) is observed. In addition, speech disorders such as echolalia and illogical speech, and poor or no eye contact are often observed [2].

Some patients may only have psychiatric symptoms, especially in relapses. In the Kayser et al. study [13], in a group of 600 patients diagnosed with autoimmune encephalitis with anti-NMDAR antibodies, some patients did not show autonomic dysfunction or neurological signs and only presented isolated psychiatric symptoms – these patients did not differ significantly in terms of age, sex, and the presence of teratoma from the population at large. All symptoms resolved after treatment [8]. Accordingly, some studies on defining specific markers related to the predicted clinical course of the disease were carried out. Currently, it seems that biochemical markers that may be important for the prognosis are: YKL-40 glycoprotein (CHI3L1 or HCgp39) and CXCL13 chemokine, the presence of which is associated with a more severe course of the disease and a poorer response to treatment [14], but the issue still requires further research.

The current diagnostic criteria are presented in Table 1.

Table 1. **Diagnostic criteria for anti-NMDAR encephalitis**

Diagnostic criteria **Anti-NMDAR Encephalitis**
Probable diagnosis:
Diagnosis can be made when all three criteria are met:
1. Sudden onset (less than 3 months) with at least 4 out of 6 major symptom groups:
– Behavioral change or cognitive impairment
– Speech disorders (acceleration, verbal reduction, mutism)
– Seizures
– Movement and posture disorders: dyskinesias, stiffness/unusual poses
– Disturbances of consciousness
– Autonomic dysfunction or central hypoventilation
2. At least one abnormal test finding:
– EEG: focal or diffuse changes (slow activity, disorganization, seizure, "delta brush")
– CSF: pleocytosis or the presence of oligoclonal bands
3. Exclusion of other causes
Diagnosis can also be made if three of the above groups of symptoms are present in a patient with teratoma
Definitive diagnosis:
Presence of specific autoantibodies, after other causes have been ruled out

Based on [24]

In 2019, Balu et al. [15] published a practical scale for the prognostic assessment of the clinical course of the disease and the patient's functioning within one year after diagnosis – the NEOS (anti-NMDAR Encephalitis One-Year Functional Status) score. The important factors are:

1. the need for ICU (intensive care unit) admission;
2. treatment delay of more than 4 weeks from symptom onset;
3. no clinical improvement after 4 weeks of treatment;
4. presence of inflammatory lesions on MRI of the CNS (magnetic resonance of the central nervous system);
5. CSF (cerebro-spinal fluid) pleocytosis > 20 cells / uL.

This scale may help identify the patients who require the most intensive supervision due to the significant severity of symptoms.

The differential diagnosis includes primarily viral neuroinfections and mental disorders. It should be emphasized that many patients, due to the dominant psychotic symptoms, stay in psychiatric wards. Ignorance of the symptomatology of anti-NMDAR encephalitis can lead to misdiagnosis (e.g. acute polymorphic psychotic disorder), the use of neuroleptics, and the understanding of the emerging symptoms of subsequent phases as a complication of antipsychotic treatment or as symptoms of neuroleptic malignant syndrome [2]. Practical clinical guidelines relevant to the diagnostic process are presented in Table 2.

Table 2. **Practical diagnostic guidelines in suspected anti-NMDAR encephalitis**

Psychotic episode: significant features of anti-NMDAR encephalitis:
Previous flu-like symptoms
Rapid onset of symptoms
Rapid onset of catatonia
Female gender
Neurological symptoms, seizure
Severe autonomic dysfunction
Presence of a tumor
Worsening of symptoms after antipsychotic treatment

Based on [7]

Additional tests/diagnostics

In the examination of the cerebrospinal fluid in the initial stages of the disease, lymphocytic pleocytosis is usually found (in studies [2, 9] in about 80-90% of patients). Increased protein concentration is found in approximately 33% of patients, and the presence of oligoclonal bands in the CSF in 25-80% of patients [9].

In MRI of the CNS, inflammatory changes are observed in 11-83% of patients, depending on the study [16]. Typical lesions are hyperintense foci in the T2 and FLAIR sequences located most often in the hippocampus, the cerebral and cerebellar cortex, the anterior basal regions, basal ganglia or in the brainstem, rarely in the medulla. The changes may be few, minor, and there is often a slight contrast enhancement of the affected areas or the meninges [2]. Progressive cerebellar atrophy seems to be an unfavorable prognostic marker [17]. In the acute phase of the disease, FDG-PET shows hypermetabolism in the fronto-temporal areas and hypometabolism in the parieto-occipital areas.

It should be emphasized that the possibility of encephalitis with anti-NMDA antibodies in a patient with no pathological changes in MRI examination of the CNS

should not be ruled out. At the present stage of knowledge, the presence of changes in the CNS MRI is not a diagnostic criterion for the diagnosis of encephalitis with anti-NMDA antibodies (Table 1).

In the EEG (electroencephalogram) test, 90% of patients have non-specific changes. The most common include slow waves and the so-called "extreme delta brush" pattern – not a pathognomonic phenomenon, but it occurs in about 30% of patients [18]. Less frequently focal changes, most often in the temporal or fronto-temporal areas, generalized paroxysmal changes and non-convulsive epileptic states are described [2].

EEG, due to its low invasiveness and greater sensitivity than MRI, seems to be a useful test and is helpful in monitoring the effectiveness of treatment and assessing the prognosis [19]. It seems that in patients with normal EEG recordings, the prognosis is significantly better, and the course of the disease itself is lighter and burdened with fewer complications and autonomic disorders, and there is less need for care in intensive care units [11].

The most sensitive and diagnosis-specific test is the presence of antibodies against NMDA receptors (NMDA receptor antibodies) in the CSF and/or peripheral blood. Despite previous reports on sufficient sensitivity of the method of determining the concentration in peripheral blood, the authors of the latest studies emphasize that the concentration of intrathecal IgG corresponds best to the severity of the disease. Also now, it seems that in milder cases, the presence of antibodies is often found only in the CSF [2, 5].

In autoimmune encephalitis with anti-NMDAR antibodies, the role of antibodies in the IgG class has been documented. They are believed to be closely related to encephalitis, while the role of antibodies in the IgM and IgA classes has so far been ambiguous. There are hypotheses regarding the role of IgM and IgA antibodies in viral infections, dementia and schizophrenia. These antibodies are also found in healthy people – even up to 10% of the population [8].

Descriptions of patients with encephalitis with anti-NMDAR antibodies confirm the glutamatergic hypothesis of psychosis related to dysfunction of the NMDA receptor. Based on previous research, the relationship between psychotic symptoms, autoimmune disorders and the role of glutamatergic receptors has been documented. This sheds new light on the problem of establishing the etiological factor in other mental diseases, in particular in schizophrenia. We know now that schizophrenia is a disease in which dysfunction of many neurotransmitters is observed. Based on the above data, it can therefore be assumed that in the future it will probably be a clinical diagnosis associated with the occurrence of specific symptoms of various etiology, including autoimmune [8].

Treatment

Quick and correct diagnosis and, consequently, the introduction of adequate immunomodulatory treatment gives the highest percentage of successfully cured patients. The effectiveness in such a situation is 75-80% [8].

In each patient, imaging tests should be performed to look for neoplasms, in particular teratoma (tests: MRI, CT, USG), and tumor markers such as: CA 125, beta-hCG, alpha-fetoprotein, and testosterone should be determined. In patients with cancers, surgical resection of the tumor is always recommended in the first stage.

Standard treatment includes steroid therapy, intravenous infusions of immunoglobulins (IVIG), and plasmapheresis. If there is no improvement, azathioprine, rituximab, cyclophosphamide or mycophenolate mofetil are used in second-line treatment [7]. Recently, there have been reports of the effectiveness of bortezomib, a proteasome inhibitor, the effectiveness of which was estimated at 55% [19]. According to current knowledge, similar efficacy of treatment with this drug is observed both in patients after tumor resection and in the absence of tumor, although it seems that patients after tumor resection require less aggressive immunotherapy.

Additionally, symptomatic treatment is carried out, including anti-epilepsy drugs such as traditionally used drugs, as well as trials of ketamine treatment [21]. In antipsychotic treatment, mainly benzodiazepines or electroconvulsive therapy are used, while treatment with atypical neuroleptics should be carried out with caution, with the awareness of the possible occurrence or worsening of extrapyramidal symptoms [22].

Due to the frequent coexistence of autonomic disorders, constant monitoring of the patient is required, and in the case of persistent bradycardia, treatment with theophylline or pacemaker implantation is recommended [23]. Symptomatic treatment is recommended in cases of hypo/hyperthermia, hypoventilation and hypersalivation.

The recovery process is slow and multi-stage in nature. Usually, in the first stage, disturbances of consciousness are the first to disappear in patients followed by an improvement in autonomic dysfunction and reduction of dyskinesias. The contact with patients, including both verbal and non-verbal functions, gradually improves and in the final stage of recovery an improvement in social and executive functions is observed. Still typical is symptom fluctuation with periods of agitation and psychotic symptoms alternating with psychomotor slowing. Also typical symptoms during the recovery period are: impulsivity, hyperphagia, hypersexuality, and hypersomnia. A characteristic symptom is amnesia of the disease period, which the authors associate with a reversible reduction of NMDA receptors in the central nervous system. On average, hospitalization during the symptomatic period takes about 3-4 months, and then the patient requires several months of rehabilitation. The authors associate the long recovery period with a lower effect of intravenous immunosuppressive therapy (steroids, IVIG, plasmapheresis) on the reduction of the level of antibodies in the cerebrospinal fluid than in the serum [10].

Prognosis

In adult patients, we have several long-term analyses, which show that after two years of follow-up, 75-78% of patients experience complete remission or the presence of minor symptoms that do not interfere with everyday functioning [25]. Relapses of the disease are observed in about 10-15% of patients [8]. The risk seems to be particularly high in pregnant women [9]. Permanent neurological deficits occur in approximately 25% of patients, while the mortality rate is estimated at approximately 4-5% [2].

In the pediatric population, the exact long-term prognosis is unknown and this issue requires further research. However, it seems that the prognosis is more serious than in adult patients, because permanent sensory or motor deficits are observed in 20-30% of patients [26]. Permanent deficits in executive functions and memory are also more frequently observed, which the authors explain as the result of the inflammatory process, often involving the structures of the hippocampus and subcortical nuclei [26]. Such patients require constant multidisciplinary therapy and systematic neuropsychological assessment [27].

Factors important in both the short-term and long-term prognosis can be divided into those related to the occurrence of specific clinical symptoms, the results of additional tests, and treatment. The most important clinical symptoms in the short-term prognosis include the presence of autonomic dysfunction and the related need for treatment in intensive care units. Cognitive impairment is the most important for long-term prognosis [27].

The analysis of the results of additional tests indicates the most important prognostic role of the EEG test and the presence of typical inflammatory changes in the MRI of the CNS, especially if they coexist with the corresponding clinical symptoms (paresis, sensory disturbances) [26]. In treatment, the most important prognostic factor is the time of initiation of immunotherapy, which – if it occurs in the early stages of the disease – is one of the most important factors improving the prognosis. On the other hand, treatment delay by more than 4 weeks is associated with a more severe course of the disease and frequent occurrence of persistent neurological deficits [26].

Although seizures and status epilepticus occur frequently in the pediatric population with anti-NMDAR encephalitis and patients require antiepileptic treatment, recent studies show that there is no need for long-term continuation of this treatment. In previous studies, the risk of epilepsy was estimated at 30-35%; currently it is 8% [12]. Therefore, according to the current state of knowledge, it is recommended to discontinue antiepileptic drugs after clinical seizures have resolved in patients with EEG improvement, who did not require treatment in an intensive care unit and did not have status epilepticus [12].

Summary

Since the description of the first anti-NMDA receptor-positive encephalitis patients, the greatest attention has been paid to the fact that because of the dominant psychiatric symptoms, these patients are misdiagnosed and not treated appropriately. At the same time, it is important to emphasize the key role of early diagnosis and prompt implementation of appropriate treatment due to the possibility of protecting the patient against the occurrence of neurological symptoms and dysautonomia in later stages, including life-threatening arrhythmias and respiratory disorders. Despite an extremely important problem, this topic is not very common in Polish psychiatric literature. This may be the reason why this disease is so rarely recognized in the Polish population. Currently, the diagnosis and treatment mainly concern patients with the most severe course or with predominant neurological symptoms [5].

Early diagnosis, symptomatic treatment and intensive care are essential factors that improve prognosis [3]. According to the latest guidelines, patients with the most severe symptoms, such as status epilepticus, respiratory failure, autonomic dysfunction, and cardiac arrhythmias, should be constantly monitored in intensive care units and guided by multidisciplinary teams including pediatric, cardiological, neurological, psychiatric, dietary, and physiotherapeutic care.

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