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Autoimmune encephalitis with anti-NMDAR antibodies – variety of clinical manifestations

Autoimmunologiczne zapalenie mózgu z obecnością przeciwciał anty-NMDAR – różnorodność objawów klinicznych

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Abstract

The aim of this study was to review the literature on the topic of diversity of clinical symptoms of autoimmune encephalitis with the presence of antibodies against *N*-methyl-D-aspartate receptors (anti-NMDAR antibodies), the diagnostic process, and treatment. The incidence of the disease is approximately 4% of all reported cases of encephalitis. Autoimmune encephalitis with anti-NMDAR antibodies manifests as a rapidly progressive encephalopathy of acute or subacute onset. It usually develops over a period of six weeks. To diagnose the disease, it is necessary to confirm a minimum of four out of six symptoms, such as behavioural or cognitive impairment, speech impairment, epileptic seizures, movement disorders, disturbances of consciousness, and autonomic dysfunction. The diagnostic process is aided by additional examinations including electroencephalography, cerebrospinal fluid examination, magnetic resonance imaging, and laboratory tests (e.g. determination of titre of antineuronal antibodies). It is not uncommon for symptoms to indicate the possibility of co-occurrence of several psychiatric conditions at the same time, leading to a delay in making a correct diagnosis. Moreover, it should be remembered that anti-NMDAR encephalitis often displays the characteristics of a paraneoplastic syndrome, and particularly often coexists with ovarian teratoma. Consequently, this option should be included in the diagnostic process. Autoimmune encephalitis with anti-NMDAR antibodies can manifest itself in many ways, often with multiple neurological and psychiatric symptoms. Quick diagnosis, as well as early targeted treatment, increase the chance of success of the therapeutic process.

Keywords: autoimmune inflammation with anti-NMDAR antibodies, anti-NMDAR antibodies, encephalitis

Streszczenie

Celem pracy był przegląd piśmiennictwa dotyczącego zróżnicowania objawów klinicznych autoimmunologicznego zapalenia mózgu z obecnością przeciwciał przeciwko receptorom *N*-metylo-D-asparaginowym (anty-NMDAR), a także procesu diagnostycznego i leczenia. Choroba ta stanowi około 4% wszystkich zgłoszonych zapaleń mózgu. Autoimmunologiczne zapalenie mózgu z obecnością przeciwciał anty-NMDAR objawia się szybko postępującą encefalopatią o ostrym lub podostrym początku. Choroba zwykle rozwija się w ciągu sześciu tygodni. Aby właściwie zdiagnozować zapalenie mózgu z obecnością przeciwciał anty-NMDAR, konieczne jest stwierdzenie co najmniej czterech z sześciu objawów, do których zalicza się zaburzenia zachowania lub funkcji poznawczych, zaburzenia mowy, napady padaczkowe, zaburzenia ruchu, zaburzenia świadomości, a także zaburzenia autonomiczne. W procesie diagnostycznym bardzo ważne są badania dodatkowe, a zwłaszcza badanie elektroencefalograficzne, badanie płynu mózgowo-rdzeniowego, rezonans magnetyczny, badania laboratoryjne (w tym oznaczenie miana przeciwciał antyneuronalnych). Nierzadko objawy wskazują na możliwość współwystępowania kilku zaburzeń psychicznych jednocześnie, co opóźnia postawienie właściwej diagnozy. Ponadto należy pamiętać, że zapalenie mózgu anty-NMDAR ma często charakter zespołu paraneoplastycznego, a zwłaszcza bardzo często współistnieje z potworniakiem jajnika, dlatego należy przeprowadzić diagnostykę w tym kierunku. Symptomatologia autoimmunologicznego zapalenia mózgu z obecnością

przeciwciał anty-NMDAR jest bardzo bogata; choroba ma różne manifestacje kliniczne i przebieg, cechuje się współwystępowaniem różnych objawów neurologicznych i psychiatrycznych. Szybka diagnoza i wczesne wdrożenie właściwego leczenia zwiększa szansę chorego na powodzenie terapeutyczne.

Słowa kluczowe: autoimmunologiczne zapalenie mózgu z obecnością przeciwciał przeciwko receptorom NMDA, przeciwciała przeciwko receptorom NMDA, zapalenie mózgu

INTRODUCTION

The underlying causes of encephalitis include neuroinfections as well as autoimmune diseases (Britton et al., 2015; Venkatesan et al., 2013). The latter constitute a group of diseases in which the host's antibodies against self-antigens are pathologically directed and expressed in the central nervous system (CNS) (Dalmau and Graus, 2018; Ramanathan et al., 2021). Autoimmune encephalitis is not uncommon. In fact, over the past two decades, a significant increase in occurrence has been observed, which is directly related to the discovery of numerous autoantibodies directed against the extracellular domains of neuroglial proteins (Gable et al., 2012; Leypoldt et al., 2015). The incidence of autoimmune encephalitis is still underestimated, as the symptoms are not characteristic. There have been reports indicating that the number of the above-mentioned inflammations may predominate over the number of infectious diseases within the CNS (Granerod et al., 2010).

Autoimmune encephalitis can be induced by antibodies against neuronal surface antigens, such as glutamate receptors activated by *N*-methyl-D-aspartate (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPAR), gangliosides GQ1b, DPPX, CASPR2, LGI1 (Newman et al., 2016). A significant difficulty in the diagnosis of autoimmune encephalitis lies in the time before the the onset of symptoms. In most of the reported cases, the period ranges from a few days to a few weeks, with an average severity of symptoms of approximately three weeks; however, there are also literature reports of chronic cases, from one up to five years (Graus et al., 2016).

HISTORY AND EPIDEMIOLOGY

Autoimmune encephalitis induced by antibodies against *N*-methyl-D-aspartate receptors (anti-NMDAR) was first described in 2007 (Dalmau et al., 2007). The prevalence of the disease is approximately 4% of all reported cases of encephalitis (Dalmau et al., 2011). In studies aimed at identifying the cause of first-time psychotic episodes, 4% of participants had a non-psychiatric background, with anti-NMDAR antibodies detected in 75% of patients (Guasp et al., 2021). The disease affects 80% of women, with an average age of onset of 21 years. In addition, in 58% of women over 18 years of age, the coexistence of ovarian teratoma has been observed, so one should remember that anti-NMDAR encephalitis might be a paraneoplastic syndrome (Iizuka et al., 2008; Lai et al., 2009; Seki et al., 2008).

SYMPTOMS AND DIAGNOSTIC CRITERIA

The disease manifests as a rapidly progressive encephalopathy of acute or subacute onset. It usually develops over a period not exceeding six weeks (Newman et al., 2016). In anti-NMDAR antibody-induced inflammation, a range of distinct symptoms can be distinguished, which are usually the first manifestations of the disease; these include delirium, amnesia, and epileptic seizures. Other complaints from the mental spectrum, such as mood disorders, behavioural disorders, psychosis, and catatonia, occur simultaneously, which is not characteristic of individual mental illnesses (Al-Diwani et al., 2019). Abnormalities are also observed in the cognitive domain, including disorientation, confabulation, confusion or forgetfulness, and in the motor sphere, particularly chorea, stereotypy, and dystonia. Dysautonomia, manifested by fluctuations in blood pressure and alternating tachy- and bradyarrhythmia, is also characteristic of the disease (Endres et al., 2020; Varley et al., 2020). All the following diagnostic criteria are required for the correct diagnosis. These relate to the initial duration of symptoms, which must be no longer than three months. In addition, it is necessary to confirm a minimum of four out of six symptoms such as behavioural or cognitive impairment, speech impairment, epileptic seizures, movement disorders, reduced level of consciousness, and autonomic dysfunction. Another diagnostic component that should be present is the confirmation by additional tests: abnormal electroencephalographic (EEG) recording or pleocytosis in cerebrospinal fluid (CSF) analysis. In addition, during the differential diagnostic process, other possible causes of the complaints presented should be sufficiently excluded (Graus et al., 2016). Moreover, because of the frequent co-occurrence of ovarian teratoma, this diagnostic option should be considered in women suspected of anti-NMDAR encephalitis.

DIVERSITY OF MANIFESTATIONS

Anti-NMDAR encephalitis may also have a different clinical picture, as exemplified by the case of a 15-year-old female patient diagnosed with neurocardiogenic syncope, who later developed episodes of altered consciousness with unexplained abdominal pain. EEG studies indicated significant abnormalities, while the overall clinical findings suggested the diagnosis of epileptic seizures with autonomic features. On further diagnosis, CSF examination revealed the presence of anti-NMDAR antibodies (Ren et al., 2019).

Another example is the case of a 32-year-old woman with epilepsy. In this case, magnetic resonance imaging (MRI) showed no pathology, but the EEG recording showed subclinical seizure changes originating in the left and right temporal lobes. Despite a good response to valproic acid, the patient exhibited unstable moods with crying fits. No improvement was obtained after the inclusion of olanzapine. In addition, the woman was observed to have significant sluggishness, while upon awakening after 20 hours of sleep, her drive was visibly increased, she presented with echolalia, retrograde and subsequent amnesia, increased muscle tone, and mild hand tremor. After the detection of anti-NMDAR antibodies in the patient's CSF and implementation of adequate treatment, remission of symptoms was achieved (Forrester et al., 2020).

Autoimmune encephalitis can also occur in males. In the case of a 68-year-old man, a sudden mental and neurological deterioration was observed, with behavioural symptoms, unsteady gait, headache, and irregular hand movements. Confirmation of the diagnosis was obtained by CSF examination (detection of anti-NMDAR antibodies). In addition, the MRI scan showed intense enhancement of the dura mater in the region of the left cerebral hemisphere (Jia et al., 2019).

There are also reports indicating a possible link between the illness and a pre-existing acute reaction to traumatic events. The case presents the story of a 14-year-old female patient who was a victim of sexual abuse five days prior to admission. The onset of symptoms was determined to be 20 days prior to admission, when the patient was observed to have lowered mood and increased irritability. After the traumatic sexual event, the girl displayed bizarre behaviour (showering with her clothes on, going out without shoes, etc.), which could suggest the onset of a psychotic disorder. On admission to hospital, mutistic behaviour was observed. Despite the absence of abnormalities on morphology, biochemistry and toxicology, the patient developed agitation and speech disorders. During hospitalisation, a diagnosis of catatonia was confirmed, manifesting as agitation with alternating stupor, mutism, grimaces, echolalia, stereotypy, talkativeness, and negativism with refusal to take food and liquids. The MRI findings were normal. Nevertheless, anti-NMDAR antibodies were found in the CSF (Bogdan et al., 2022).

Pregnant women can be affected by the condition, too; placental passage of anti-NMDAR antibodies is possible in both symptomatic and asymptomatic patients. There are reports of an infant with decreased respiratory effort, reluctance to eat and, moreover, movement disorders observed from the first days after birth. The infant's mother had been diagnosed with autoimmune encephalitis with anti-NMDAR antibodies 18 months earlier (Chourasia et al., 2018).

The disease can also be induced by herpes simplex virus (HSV) infection. One example is that of a 23-year-old female patient who presented with disorientation, irritability and cognitive deficits following an epileptic seizure. MRI in diffusion-weighted imaging (DWI) sequence showed hyperintense lesions in the right temporal lobe region (Hu et al., 2021).

The possibility of co-occurrence of neuromyelitis optica spectrum disorder (NMOSD) and anti-NMDAR encephalitis has also been reported. A 61-year-old woman reported headache, visual disturbances, dysuria, and weakness in her limbs, in addition to respiratory failure, hypotension, and finally coma. MRI revealed abnormalities in the left temporal lobe, midbrain, bilaterally periventricular, medulla oblongata, and cervical and thoracic segments of the spinal cord. Anti-NMDAR and anti-AQP4 IgG antibodies were found in the CSF (Tao et al., 2019). In another case, involving a 38-year-old man hospitalised for recurrent epileptic seizures, MRI revealed an initial demyelinating lesion located in the brainstem, followed by the detection of a new serpentine lesion within the cerebral cortex. The CSF showed the presence of both anti-NMDAR and anti-MOG antibodies (Ren et al., 2021).

We observed a typical case of coexistence of anti-NMDAR encephalitis with ovarian teratoma in our medical practice in a 29-year-old woman hospitalised for psychotic disorders in the psychiatry department. Due to the lack of improvement after the use of neuroleptics, the patient was consulted by a neurologist. The MRI of the head was normal, but the CSF examination revealed pleocytosis (33 cells/mm^3) and the presence of anti-NMDAR antibodies. The patient underwent extensive diagnostics for cancer; ultimately, the consulting gynaecologist suspected a right ovarian teratoma, which was confirmed by histopathological examination. After the treatment (steroids, intravenous immunoglobulins) and gynaecological surgery, the patient's condition improved (Sierakowska et al., in press).

AUTOIMMUNE ENCEPHALITIS WITH ANTI-NMDAR AND COVID-19

Neurological complications due to COVID-19 in hospitalised patients are common. Nervous system symptoms can occur both during the course and after the infection. The most common complications include headache, myalgia, encephalopathy, and dizziness. There are also reports of autoimmune encephalitis developing from SARS-CoV-2 virus infection (Stoian et al., 2022). Currently, there is insufficient knowledge of autoimmune neurological diseases following COVID-19 infection. In the majority of cases with severe coronavirus infection, no antibodies to SARS-CoV-2 virus have been found in the CSF (Grimaldi et al., 2020; Guilmot et al., 2021). Based on the available literature, the most common autoimmune encephalitis with COVID-19 co-infection is that with anti-NMDAR antibodies (Stoian et al., 2022). The course of the disease was not always characteristic. In one of the reported cases, a 50-year-old man, with no prior treatment for somatic diseases except mild hypertension, was admitted to hospital because of delirium and confabulation. On the day of admission, the patient presented with fever

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(38°C), without leucocytosis or elevated C-reactive protein levels or respiratory symptoms. After four days of hospitalisation, focal convulsions with impaired consciousness and accompanying orofacial dyskinesia/automatisms were observed. The MRI was normal. Despite pharmacotherapy with valproic acid and lacosamide, drug-refractory status epilepticus developed, requiring treatment in the intensive care unit. CSF examinations revealed pleocytosis, and the anti-NMDAR antibody test was positive. Also, polymerase chain reaction (PCR) test was positive, confirming SARS-CoV-2 infection (Monti et al., 2020). In the literature, there is also a case report of autoimmune encephalitis as a result of vaccination against SARS-CoV-2. The patient was a 20-year-old woman who was admitted to hospital with urinary incontinence one week after receiving the first dose of the Pfizer-BioNTech vaccine. The family reported the woman's increasing anxiety attacks, disturbances of consciousness, and her misconception that she had kidney and gastrointestinal disease. In addition, the patient presented with hypochondriac and referring delusions, transient aphasia and motor dysfunction, in addition to being bizarre in her behaviour. The physical examination did not show any features of COVID-19; only hypertension and tachycardia were observed. Haematological and urinalysis results remained within normal limits. Increasing symptoms of psychosis remained unresponsive to pharmacological treatment. During the hospitalisation, catatonia developed and epileptic seizures occurred. The MRI was normal, but pleocytosis and anti-NMDAR antibodies were present in the CSF (Flannery et al., 2021). Recent reports indicate that patients with genetic susceptibility after SARS-CoV-2 infection may develop CNS damage due to antibodies targeting viral particles, driven by molecular mimicry in the coronavirus. Moreover, during both mild and severe COVID-19, the occurrence of lymphopenia may contribute to a reduction in the number of regulatory T cells and, at the same time, cause overactivation of the immune system (Sheu and Chiang, 2021). In a case of a 28-year-old man, two weeks after the diagnosis of COVID-19, mental deterioration was observed, which manifested as chaotic speech, excessive lethargy, and auditory hallucinations; in addition, the patient had suicidal thoughts, generalised tonic-clonic seizures, and catatonia. Despite the absence of pathology on CSF examination, MRI showed bilateral hyperintensities of the anterior cingulate cortex as well as the temporal lobes. EEG revealed subcortical dysfunction in the frontal, temporal, and occipital regions. On further diagnosis, positive titres of anti-NMDAR and anti-GAD65/67 antibodies (characteristic of limbic encephalitis) were obtained (Titulaer et al., 2013a, 2013b). A hypothesis was put forward that suggested that the SARS-CoV-2 molecule activated both cellular and humoral immunity, which may have contributed to the production of antibodies mimicking both anti-NMDAR and anti-GAD65 (Al-Sarraj et al., 2021).

TREATMENT

Glucocorticosteroids are used in the treatment of autoimmune encephalitis. The first-choice drug is methylprednisolone, initially given intravenously and then orally. If there is no improvement after treatment with glucocorticosteroids or there are contraindications to their use, intravenous IgG therapy is recommended. Improvement has also been reported after rituximab and cyclophosphamide treatment. If concomitant cancer is diagnosed, oncological treatment is recommended. Furthermore, benefits of biologic treatment have been observed, with drugs such as tocilizumab, alemtuzumab, methotrexate, bortezomib, azathioprine or mycophenolate mofetil being used (Graus et al., 2016; Valadez-Calderon et al., 2022). Psychiatric treatment should be initiated in patients with psychotic symptoms (based on atypical neuroleptics, due to the possibility of extrapyramidal symptoms), and it is important that dose escalation is gradual (Mohammad et al., 2016). Benzodiazepines are recommended for the treatment of catatonia (Lancaster et al., 2011). Despite the lack of randomised studies on the efficacy of catatonia treatment, there are reported cases where, in the presence of anti-NMDAR antibodies in the CSF, clinical improvement was obtained following electroconvulsive treatments (Olaleye et al., 2021).

PROGNOSTIC FACTORS

Based on observations, the clinical picture of autoimmune encephalitis with anti-NMDAR antibodies varies depending on individual factors. Studies report that younger age correlates with a milder course of the disease (Zhang and Fang, 2018). Age above 12 years is a predictor of a better prognosis, while children under the age of three years have the best chance of complete recovery (Zekeridou et al., 2015). Other reports indicate a relationship between prognosis and severity of complaints. Milder symptoms, recognised as a condition not requiring hospitalisation in the intensive care unit, indicated a successful prognosis (Wang et al., 2019). It is worth noting that factors influencing mortality levels also include a Glasgow score of up to eight points (Chi et al., 2017). A multicentre randomised study showed that patients who had a significant decrease in anti-NMDAR antibodies within one month were more likely to achieve complete remission (Gresa-Arribas et al., 2014). In addition, several new biomarkers with a potential prognostic value have been reported. These include C-X-C chemokine 13 (CXCL13), extracellular mitochondrial DNA, interleukin 17 (IL-17), YKL-40, neurospecific enolase (NSE) and calcium-binding protein S100B (S100B). High values of the listed biomarkers in the CSF are associated with a weaker response to immunotherapy (Chen et al., 2018; Peng et al., 2019; Zeng et al., 2018). A cohort study of 577 participants showed that early immunotherapy might result in more favourable clinical outcomes (Titulaer et al., 2013a, 2013b). This is supported by the outcome of implementing immunotherapy in five children within a week of onset, four of whom achieved complete remission of the disease (Byrne et al., 2014). Both early treatment and rapid diagnosis (in not more than eight weeks after the onset of symptoms) have a positive effect on the final therapeutic outcome

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(Wright et al., 2015). However, more sensitive diagnostic tools are needed to improve the diagnosis and treatment of autoimmune encephalitis with anti-NMDAR antibodies.

CONCLUSIONS

Autoimmune encephalitis with anti-NMDAR antibodies can manifest in a variety of ways, often with multiple neurological and psychiatric symptoms. Quick diagnosis, as well as early targeted treatment, increase the chance of success of the therapeutic process.

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

Author contributions

Original concept of study: AS. Writing of manuscript: AS, MR. Critical review of manuscript: BŁR. Final approval of manuscript: BŁR.

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