



Autoimmune anti-N-methyl-D-aspartate (NMDA)-receptor encephalitis as a rare cause of complex psychiatric and neurologic manifestations. Case report and literature review

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Paluch Z, Borys M, Krawczyk M, Duda P. Autoimmune anti-N-methyl-D-aspartate (NMDA)-receptor encephalitis as a rare cause of the complex psychiatric and neurologic manifestations. A case report and review of the literature. J Pre-Clin Clin Res. 2022; 16(3): 75–78. doi: 10.26444/jpcrr/152424

Abstract

Anti-N-methyl-D-aspartate (NMDA)-receptor encephalitis is a rare autoimmune disease associated with antibodies against the NMDA receptors in the central nervous system. In more than half of patients, the disease coexists with ovarian teratoma. Most patients develop a multistage illness that progresses from psychosis, cognitive dysfunction, and seizures, into a state of unresponsiveness with catatonic features often associated with a movement disorder, autonomic instability, and central hypoventilation. The work presents a case of a 20-year-old female who was transferred to an intensive care unit from the Department of Psychiatry, due to a worsening state of consciousness with symptoms of respiratory failure and hemodynamic instability. In the previous clinic, the patient was treated for catatonic schizophrenia, with no results. The diagnosis of autoimmune encephalitis was made on the basis of the result of cerebrospinal fluid, in which antibodies to NMDA receptors were detected.

Key words

respiratory insufficiency, catatonic schizophrenia, anti-NMDA receptor encephalitis

INTRODUCTION

Anti-N-methyl-D-aspartate (NMDA)-receptor encephalitis is a rare autoimmune disease associated with IgG antibodies against the NR1 subunit of the NMDA receptors in the central nervous system (CNS) [1–3]. NMDA receptor encephalitis most often affects women in the age range 25–35 years. In more than half of all patients, the disease co-exists with neoplasm, mainly ovarian teratoma [3, 4]. Most patients with anti-NMDA receptor encephalitis develop a multistage illness that progresses from psychosis, memory deficits, cognitive dysfunction, speech dysfunction and seizures, into a state of unresponsiveness, with catatonic features often associated with a movement disorder, dyskinesia, rigidity, autonomic instability and central hypoventilation [1, 5, 6, 7, 8]. At onset, about 90% of all patients have prominent psychiatric or behavioural symptoms that can be difficult to differentiate from a primary psychiatric disease, such as schizophrenia or bipolar disorder [5]. The gold standard diagnostics is a serum or cerebrospinal fluid (CSF) sample screening for antibodies to the NMDA receptor subunit [2].

First-line treatment includes rapid immunomodulating / immunosuppressive therapies with corticosteroids,

immunoglobulin infusion (IVIG) and plasmapheresis (PLEX), and second-line treatment with rituximab and cyclophosphamide – with good therapeutic effect [8, 9]. Early diagnosis and implementation of appropriate treatment give hope for a better prognosis in anti-NMDA receptor encephalitis patients, and even in most patients, full recovery is achieved, with no memory of the events or the illness [6]. Due to good treatment options, it is important that clinicians, including psychiatrists, neurologists, neurosurgeons and anesthesiologists, consider autoimmune anti-NMDA receptor encephalitis in the differential diagnosis of psychiatric patients that frequently require mechanical ventilation.

The study aimed to present a case report, diagnosis and possible treatment modalities for patients with anti-NMDA receptor encephalitis.

CASE REPORT

In May 2020, a 20-year-old female in the 1st trimester of pregnancy was admitted to the Department of Neurology presenting with loss of consciousness, limb tremors, headaches and delusions. During hospitalization, the patient was periodically agitated, uttered delusional content, was aggressive and displayed illogical contact. In an MRI examination of the head, there were no features of brain damage. Laboratory results were also normal. In the patient's history, it was established that in 2014, the

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Received: 12.05.2022; accepted: 26.07.2022; first published: 08.08.2022

patient was hospitalized in a Paediatric Hospital because of seizures that occurred just after an upper respiratory tract infection. She was later hospitalized three times due to headaches, convulsions, hallucinations and abnormal behaviour dysfunctions. No changes were perceived in the image diagnosis.

Due to the intensified symptoms of psychosis, psychomotor agitation and the lack of logical contact with the patient, she was transferred to the Psychiatric Department. The hospitalization lasted 30 days. During the stay in the hospital, verbal contact with the patient was sometimes illogical, and there was a problem with consciousness. An initial diagnosis was catatonic schizophrenia or a schizoaffective disorder. Despite the treatment applied, a progression of psychiatric disorders was observed, and periodic episodes of apnea occurred. Results of the CSF analysis revealed lymphocytic pleocytosis and an increased protein level (Tab. 1).

Table 1. Cerebrospinal fluid (CSF) – results of the described patient

Parameter	Patient	Normal range
White blood cells (WBC) per mL	12 ↑ (mononuclear leukocytes 100%)	0–5
Protein (mg/dL)	63.13 ↑	<45
Glucose (mg/dL)	55	45–80
Chloride (mmol/L)	124	115–130

During her hospital stay, she miscarried. A few days later, the patient was transferred to the Intensive Care Unit (ICU), due to her deteriorating state of consciousness with symptoms of respiratory failure and haemodynamic instability. During the time in the ICU, her condition was assessed as medium-severe (Glasgow Coma Scale score 9), without verbal contact. The cardiovascular system was monitored haemodynamically and she required minor support on the first day through the infusion of noradrenaline. A neurological examination revealed a positive sign of a stiff neck and excessive knee reflexes. Results of the CT examination revealed abdominal

cavity and pelvis without deviations. However, CT examination of the chest revealed ground glass opacity of the lower lobe of the left lung, and the presence of speckled shadows of inflammatory parenchymal densities – mainly in the posterior basilar segment. Suspecting autoimmune encephalitis or antiphospholipid syndrome, antibodies against NMDA, GABA, AMPA, ACA and anti-b2-glycoprotein receptors were determined in CSF and in the serum of the patient. While awaiting the result, empirical intravenous steroid therapy was started – without clinical improvement. The patient was transferred to the Psychiatric Department for further treatment.

Two weeks later, a positive result was obtained from the laboratory for the presence of antibodies to NMDA receptors in CSF and serum. Based on the result, a diagnosis was made – NMDA-receptor autoimmune encephalitis. The patient was immediately transferred to the Intensive Care Unit to undergo a cycle of plasmapheresis. Upon admission, agitation and restlessness were observed, followed by progressive mutism and somnolence, which were the predominant symptoms of the disease. During the patient's 16-day stay in the ICU, a series of therapeutic plasma exchanges was performed (12 in total), 3 doses of rituximab were administered, and diagnostics continued to identify the source of antibodies against the NMDA receptor (imaging diagnostics, hysteroscopy, diagnostic laparoscopy). Exploratory laparoscopy was performed to collect material for cytological examination of the Douglas cavity fluid and ovarian cyst. A peritubular (paratubular?) cyst was excised and fluid was collected from the Douglas's sinus for cytological examination. Histopathological examination revealed the presence of a simple ovarian cyst, teratoma, was excluded. During hysteroscopy of the posterior wall of the uterus, the mucosal elevation was removed, which may correspond to the endometrial polyp or trophoblast remnants. After the immunosuppressive treatment a significant improvement in the patient's condition was seen, and she was transferred to the Department of Psychiatry for continuation of treatment. The case report timeline is presented in Figure 1.

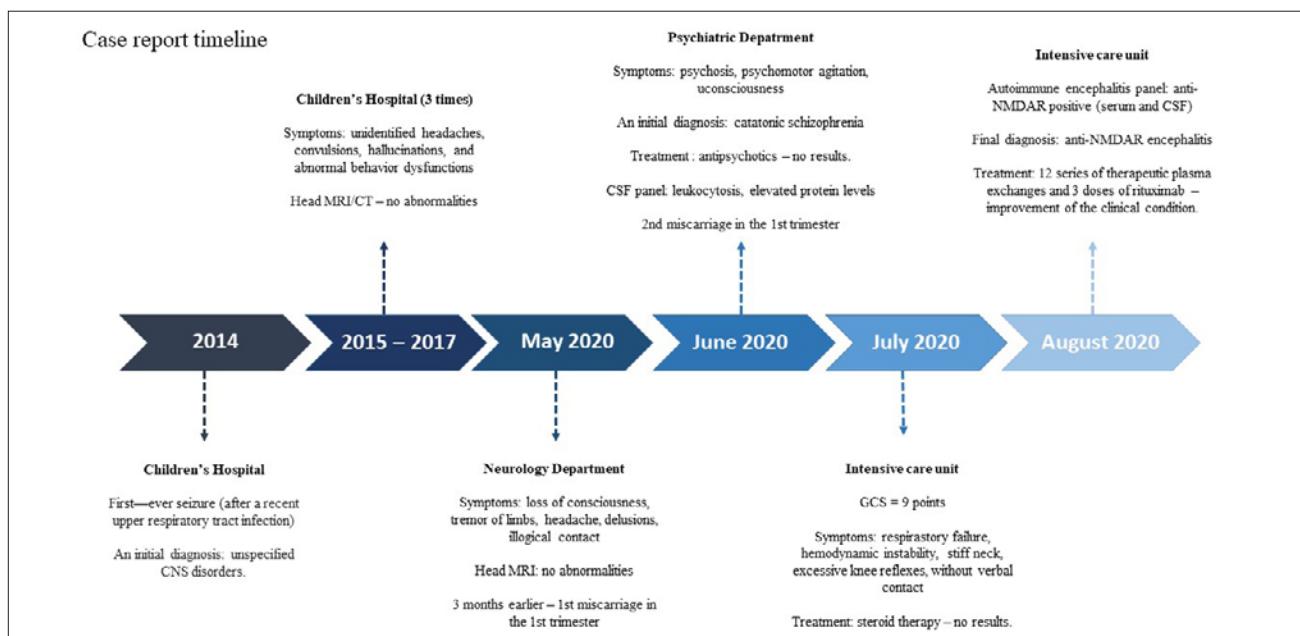


Figure 1.

DISCUSSION

Anti-NMDA receptor encephalitis was first described by Dalmau et al. [1] in 2007, among 12 female patients with ovarian or mediastinal teratoma. Since then, two triggers of anti-NMDA receptor encephalitis have been confirmed – tumours and herpes simplex encephalitis (HSE) [5, 10]. Among female patients aged 18–45, teratoma is the most common cause and contributes to 58% of all cases [11]. In teratomas containing mature or immature neural tissue, NMDA receptors expressed on those cells are suspected of being a causative agent of autoimmune reaction [11]. This case report presents the case of a 20-year-old female admitted to the Intensive Care Unit (ICU), with a preliminary diagnosis of catatonic schizophrenia.

Diagnosis of anti-NMDA receptor encephalitis is confirmed when specific autoantibodies are detected. In doing so, CSF was shown to be highly sensitive, and specific, compared to serum samples [12]. What is more, CSF antibodies titer were shown to better correlate with clinical outcomes [11], and appear earlier after HSE, compared to serum titers [11]. Interestingly, in most cases, serum titer analysis display higher values than CSF titers [13].

In presented case, the diagnosis was probably significantly delayed. The first onset of symptoms that could be linked to the NMDA receptor encephalitis, including behaviour disorder and epileptic seizures were reported six years before admission to the ICU, during the hospitalization in Children's Clinical Hospital after upper respiratory tract infection. Moreover, the first hospitalization that could be linked directly to signs of impaired consciousness and behaviour began 40 days before admission to the ICU. The initial diagnosis was catatonic schizophrenia. During ICU hospitalization, the latter diagnosis of anti-NMDA receptor encephalitis was made, which took another nine days.

If a tumor is detected, treatment options consist of immunosuppression and tumour resection ([12]). In addition to tumor resection, first-line immunotherapy options are intravenous steroids, intravenous immunoglobulin G or plasma exchange [12]. If no clinical improvement is seen, second-line therapies are introduced, including rituximab, cyclophosphamide, or both [12]. Alternative first-line therapy, suitable especially for patients with severe disease, consists of rituximab combined with intravenous steroids and intravenous Immunoglobulin G or plasmapheresis.

The largest retrospective study concerning treatment outcomes of anti-NMDA receptor encephalitis was performed among 501 patients, 94% of whom were treated with first-line immunotherapy [9]. Accordingly, 394 of 501 patients achieved a good outcome during the first 24 months; however, 30 of the 501 patients died [9]. Recent data indicate that 12% of all patients have clinical relapses during 24-months of follow-up [9], and 67% of the relapses are less severe than the initial episode [9]. Relapses can occur over a long period of time, in some cases after several years [14]. Patients with a tumour had a lower frequency of relapses, compared to patients without tumours [9].

In the presented case, after the second admission to the ICU, during the 16-day hospitalization, the patient received 12 cycles of plasmapheresis and three doses of rituximab, with a gradual clinical improvement.

70% of all anti-NMDA receptor encephalitis patients are admitted to ICUs [5]. In order to assess the probability of

poor functional status at one year, Balu et al. [15] created an anti-NMDAR Encephalitis One-Year Functional Status (NEOS) score. Using a multivariate regression model, they showed that ICU admission, treatment delay >4 weeks, lack of clinical improvement within four weeks, abnormal MRI and CSF white blood cell count >20 cells/ μ L, were independent predictive factors of an unfavourable one-year outcome [15]. These aspects, along with a good response to immune therapies, emphasize the importance of quick and accurate diagnosis [16].

According to a histopathological examination of the uterine cavity and peritubular cyst samples, no teratoma was found in the described patient. As stated previously, ovarian teratoma is the most common cause of NMDA receptor encephalitis in female patients aged 18–45 [11,17], and screening for ovarian tumours should always be performed [17]. In addition, cases have been reported of ovarian teratomas being detected years after the presentation of anti-NMDA-receptor encephalitis symptoms [18]. For this reason, for young patients without detectable tumours, it is recommended to screen for ovarian teratomas with pelvic MRI or ultrasound every six months for four years [2]. The possible occurrence of neoplasm in the presented patient with recognized autoimmune anti-NMDA receptor encephalitis obliged discerning observation.

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