Autoimmune anti-N-methyl-D-aspartate receptor encephalitis — the current state of knowledge based on a clinical case

Rafał Wójtowicz, Magdalena Krawiec, Piotr Orlicz

Department of Anaesthesiology and Intensive Care, Central Teaching Hospital in Warsaw, Ministry of Interior and Administration (MI&A), Poland

Abstract

The aim of this article is to conduct an overview of the current state of knowledge about patients presenting anti-N-methyl-D-aspartate receptor encephalitis associated with neoplastic process, as well as diagnosis and treatment. This disease concerns mainly young women and correlates with ovarian teratoma. Most important problems seems to be the difficulties in making a proper diagnosis ensuing from the rarity of this syndrome, the period from the appearance the first symptoms to starting treatment and the correct handling of intensive care complications. There are only a few articles describing severe, complicated cases of this type of encephalitis, requiring treatment in an intensive care unit.

Key words: autoimmune encephalitis; anti-N-methyl-D-aspartate receptor; ovarian teratoma; intensive care

Autoimmune anti-N-methyl-D-aspartate (NMDA) receptor encephalitis was first described in 2007 [1]. The disease belongs to rare causes of limbic encephalitis and is typically diagnosed in young female patients with paraneoplastic ovarian teratomas [3].

The blocking of NMDA receptors in the brain leads to characteristic symptoms of the disease. Inactivation of GABA-energic neurons results in psychotic disorders, involuntary movements, fasciculation, and nystagmus whereas the effects on the respiratory centre in the brain stem can cause breathing difficulties requiring mechanical ventilation. Moreover, patients present with symptoms resulting from the influence on the autonomic nervous system, e.g. hypersalivation, arrhythmias or arterial hypertension. The impaired NMDA receptor function is functional in nature and reversible in the majority of cases; therefore, correct diagnosis and quick implementation of treatment, involving tumour removal and immunotherapy, are likely to provide beneficial therapeutic effects [4]. About 75% of patients diagnosed with autoimmune anti-NMDA receptor encephalitis fully recover or experience only minor disease-related sequelae. The remaining percentage sustains severe deficits whereas 7% of cases end in death [2, 5].

CASE REPORT

A 23-year-old previously healthy patient was admitted to the hospital of infectious diseases due to headache, fever up to 39° C persisting for 48 hours, disorders of consciousness, vomiting and photophobia. Three days before the onset of fever, the patient reported headache, general malaise and cattarrhal infection. The imaging examinations performed on admission, i.e. computed tomography (CT), CT with contrast and magnetic resonance imaging (MRI), did not demonstrate any abnormalities. The cerebrospinal fluid (CSF) showed pleocytosis — 200 µL⁻¹ (reference range 0–5) and elevated protein concentration — 91.2 mg dL⁻¹ (reference range 20–40), which was of interest. A peripheral blood test revealed: haemoglobin concentration — 12.8 g L⁻¹, white blood count (WBC) — 6.86 G L⁻¹ (the history taken from the patient’s family disclosed her congenital susceptibility to leucopenia), platelet count (PLT) — 154 G L⁻¹. Viral cerebrospinal meningitis was suspected; although the aetiological factor was not confirmed, antibacterial and antiviral therapy was instituted. During the subsequent hospitalisation days, disorders of consciousness became aggravated, while psychomotor agitation, confusion and anxiety increased. On hospitalisation day 5, the patient developed acute respiratory failure, was intubated and transferred to
the ICU. On ICU admission, the patient’s condition was extremely severe — the Glasgow Coma Scale (GCS) score — 9. Since respiration was inefficient, the lungs were mechanically ventilated. Treatment against probable pathogens causing cerebrospinal meningitis and encephalitis was continued; due to an atypical course of disease, further diagnostic procedures were carried out in search of CNS pathologies. During the entire period of hospitalisation, the patient showed enhanced motor activity despite sedation with high doses of drugs and severe hypersalivation. After 14 days of mechanical ventilation, a tracheotomy was performed. Since the aetiological factor of CNS infection was still not confirmed and the disease picture was not typical, atypical causes of encephalitis and cerebrospinal meningitis were looked for. Tests for the presence of NMDA receptor (NMDAR) antibodies in serum were performed and the results were positive. The patient was diagnosed with autoimmune anti-NMDA-receptor encephalitis. Furthermore, an abdominal ultrasound (US) showed a left appendageal tumour. After over one month of hospital treatment, the patient was referred to the ICU of a higher referential level centre for further diagnostic procedures and multi-profile treatment.

On admission to our hospital the patient was in extremely severe condition, unconscious, under deep sedation and unresponsive to stimuli. The muscular tone was decreased, the pupils were medium wide, reactive; the left pupil was slightly wider than the right. Facial myoclonus was observed despite the continuous infusion of valproic acid. Moreover, the patient had severe hypersalivation requiring continuous aspiration. Respiration was inefficient, the lungs were mechanically ventilated yet the cardiovascular system was stable. On day 2, the patient was examined by a gynaecologist; a transvaginal ultrasound was performed, which confirmed the presence of a left appendageal tumour and the patient was scheduled for surgery. The ovarian tumour was removed laparoscopically (according to the histopathological findings — teratoma immaturum, its texture containing skin cyst elements plus foci of bony, glial tissue, mature glandular structures with single, small foci of neuroglia (the largest of which — about 2 mm in diameter). During further hospitalisation days, the patient was relatively haemodynamically stable, with a tendency to high values of arterial pressure and tachyarrhythmia. Several short-lasting arrhythmias were observed, including asystole, which subsided after a short external cardiac massage. Moreover, airway hyper-reactivity maintained; even slight manipulations within the tracheostomy tube led to increased bradycardia. Since the admission, hyperthermia, most likely of a central origin, persisted, although there were no laboratory and clinical indices of infection.

After ovarian tumour removal, a consultation panel consisting of a neurologist, nephrologist and gynaecologist recommended plasmapheresis to accelerate the elimination of antibodies against NMDA receptors. In the dialysis centre, 5 courses of plasmapheresis were carried out (day 5, 7, 9, 12, and 14). Subsequently, immunoglobulins were started (5 doses of a non-specific human immunoglobulin at a dose of 0.5 g kg⁻¹ on days 17, 18, 19, 20 and 21). In the initial period, the patient showed severe psychomotor agitation, myoclonias and tremors, which were difficult to control despite the use of many combinations of sedatives and antiepileptic drugs. Finally, the number and severity of myoclonias were reduced after tetrabenazine combined with quetiapine and baclofen (due to increased muscle tone). During intense psychomotor agitation, the patient underwent multiple EEGs, which did not explicitly confirm the epileptic brain activity (except for one electroencephalogram).

On day 20, the patient developed sepsis caused by Acinetobacter baumannii, combined with severe leucopenia to 0.15 G L⁻¹ without neutrophils in the smear. Targeted antibiotic therapy was initiated together with filgrastim (stimulating the growth of granulocytes), which improved the patient’s general condition; the absolute neutrophil count increased and the infection indices normalized.

On day 29, a medical consultation took place (comprising an anaesthesiologist, neurologist, oncologist, nephrologist) and immunosuppressive treatment was decided upon. After obtaining the approval of the bioethics committee, on day 37, the patient received cyclophosphamide at a dose of 1000 mg together with a mucolytic agent (mesna); moreover, steroid therapy with methylprednisolone was started at a dose of 50 mg/day. On day 38, 45 and 52 rytuxamab was added (a human-mouse monoclonal antibody) at a dose of 500 mg each. The final planned dose was withheld due to sepsis (day 44 and 59) induced by ESBL⁺ Klebsiella pneumoniae, methicillin-resistant Staphylococcus aureus (MRSA), HLAR GE Enterococcus faecalis and Acinetobacter baumannii, which most likely originated from the urinary system. Empiric and broad-spectrum antibiotic therapy was applied, followed by targeted therapy according to the culture results; the patient’s clinical state improved and inflammatory parameters decreased after about two weeks of treatment.

On day 72, the patient developed a complication in the form of infectious endocarditis (IE) with vegetations on the lateral leaflet of the tricuspid valve. Targeted antibiotic therapy was initiated and continued for 4 weeks; simultaneously, the course of IE was monitored ultrasonographically. Echocardiography visualised post-IE moderate tricuspid incompetence; the wave located in the posterior part of the valve, no features of pulmonary hypertension, widened cardiac cavities and venostasis. On day 106, antibiotic therapy was completed and on day 115 antifungal treatment was started as a part of empiric therapy for IE (no specific fungal species was cultured).
Until day 33, the patient was unconscious, responsive to stimuli, without logical contact. Her neurological condition gradually improved. She regained consciousness, hypersalivation subsided and the tendency to hyperthermia decreased. Moreover, psychomotor agitation and involuntary movements of the limbs and the face gradually diminished. On day 31, the patient was weaned off the ventilator and expired spontaneously with oxygen supplementation through the tracheostomy tube, including a period of a second bout of sepsis and IE. About day 80, simple communication with her was possible; she followed simple instructions and directed her eyes to the speaking individual. The contact slowly became increasingly logical. On day 90, when the tracheostomy cuff was released, she tried to articulate single words and on day 105 the tube was removed. Intensive neurological rehabilitation was initiated. Natural oral nutrition was attempted, with the patient having been fed earlier through the Flocar tube and parenterally. During the entire period of hospitalisation, intensive motor rehabilitation was applied. Over subsequent days, the neurological condition of the patient further improved until, finally, the patient became conscious, in full logical contact, answering questions, solving psychological tests. Although pre-disease permanent memory was well preserved, recent memory was negatively affected. The patient eagerly read books but did not remember what she had read the previous day. Interestingly, the patient recalled the PIN number to her cell phone and unblocked it unaided after 4 months. She was periodically agitated; her mood was lowered despite the use of antidepressants. Sleep difficulties occurred. With the improvement of her neurological condition, motor rehabilitation was intensified; she gradually assumed an erect position at the bedside and finally started to walk, aided by a physiotherapist. One month after discharge from the ICU, the patient was able to walk unaided. She was examined neurologically, psychiatrically, psychologically and by a neuro-speech therapist multiple times.

During hospitalisation, the level of anti-NMDA antibodies was determined in blood and CSF. The baseline level was observed at dilutions 1:10, 1:100 and 1:1000 (a strong reaction). After ovarian teratoma removal and 5 cycles of plasmapheresis, the serum level decreased on day 15; at dilutions of 1:10 and 1:100 — a strong reaction; and at 1:1000 — the absence of antibodies. This level was found during the follow-up examination one month after the employment of immunosuppressive treatment. Two months after the discontinuation of immunosuppressive treatment, anti-NMDA antibodies were still present — at a dilution of 1:10 — a strong reaction; 1:100, a weak positive reaction; and 1:1000 — no reaction. According to the literature data, the level of antibodies is not directly correlated with the clinical condition of patients and can remain high long after recovery, more commonly in CSF than in serum [2]. The next result during the second month after ICU discharge did not show changes — serum concentration remained high.

Flow cytometry of blood and CSF seems equally reliable. Pre-immunosuppressive therapy cytometry demonstrated a predominance of the population of CD4+/HLA DR+ T lymphocytes and macrophages with single acidophilic granulocytes as in autoimmune encephalitis, which was consistent with the clinical diagnosis. During the second month after the application of immunosuppressive therapy, the follow-up cytometry revealed the absence of CD20+/CD19+ B lymphocytes.

On day 85, PET-CT was performed to assess the radicality of treatment and metabolic activity of CNS. The findings demonstrated no changes of the active proliferative process; marker accumulation in the base nuclei and cerebral cortex was found to be symmetrically higher. Moreover, increased marker accumulation was observed at the border of the insula and the left superior temporal gurus (less pronounced in the delayed examination). On day 120, a trephine biopsy of bone marrow was performed due to a tendency to recurrent leucopenia, which evidenced that the likely cause is an autoimmune reaction.

After 160 days of hospitalisation, including 127 days of ICU treatment, the patient was discharged from hospital (at the request of the family) in a stable general condition, conscious, in full logical contact, efficient respiration and circulation. The following were recommended: continuation of treatment, 24-hour care, monitoring of vital parameters intensive rehabilitation, as well as psychiatric and haematological examinations. According to her parents, in the home setting the patient’s condition further improved. Sleep-related problems have gradually subsided, recent memory has been better. The patient has been undergoing intensive physical rehabilitation and speech therapy and is becoming self-independent; she can prepare meals unaided, exercises eagerly and has recommenced her study of law and English. In the near future, she plans to continue her studies. However, she is still unable to recall the entire disease-related period.

**DISCUSSION**

Limbic encephalitis, whose type is autoimmune encephalitis related to the presence of anti-NMDA antibodies, was first described by Brierley et al. [6] in 1960 as paraneoplastic encephalitis affecting the limbic regions (hippocampus, thalamus, hypothalamus, corpus amygdaloideum) associated with lung, breast, ovarian, uterine, stomach, kidney, urinary bladder and large intestine cancers. Encephalitis has been suggested as being induced by autoaggression against limbic system antigens. In 2001, two cases of limbic encephalitis associated with anti-potassium channel
antibodies were described; in 2003, a NR2 subunit of the anti-NMDA-receptor antibody was found in the brain of some patients with acute encephalitis, including the limbic type. The role of inflammatory and immunological processes has been studied by many medical circles [6]. To date, 577 cases of this type of encephalitis have been described worldwide [5].

In 2005, the syndrome of psychiatric symptoms with consciousness disorders and hypoventilation of a central origin was described in 4 young women with the diagnosis of ovarian teratoma [7]. The breakthrough year was 2007 when Dalmau et al. [1] identified this syndrome as autoimmune encephalitis associated with the presence of anti-NMDA receptor antibodies. NMDA receptors are located in the hippocampus and forebrain, and are glutamate receptors. This type of a receptor is selectively activated by N-methyl-D-aspartate acid; it is ionotropic and conducts cations of sodium (Na⁺), potassium (K⁺), and calcium (Ca²⁺). Beside glutamate, the activation requires the attachment of glycine or serine. Ovarian teratoma is the most common cancer inducing the formation of anti-NMDA receptor antibodies by the immune system due to the presence of various types of tissues in the tumour texture. In our patient, neuroglial cells were present in tumour structures. The generated antibodies block the NR1 subunit of the NMDA receptor in the brain inducing inflammation, which predominantly manifests as impaired memory, behaviour and consciousness, as well as seizures. Due to this atypical presentation of symptoms (psychiatric symptoms predominate), the profile of patients (relatively young women between the second and fifth decade of life), normal or completely atypical MRI images and the presence of mild ovarian cancer, autoimmune encephalitis-associated anti-NMDA receptor antibodies is unique among the cases of paraneoplastic encephalitis [1].

The fact which is characteristic of autoimmune encephalitis associated with anti-NMDA receptor antibodies is that it usually affects previously healthy young women who suddenly develop emotional disorders [3]. There are several stages of the disease and recovery. About 70% of patients present prodromal syndromes, such as headache, nausea, diarrhoea, fever or symptoms of upper respiratory infections; within the next few or several days, the psychiatric symptoms develop, e.g. mania, paranoia, in many cases — anxiety, less commonly disorders of memory or stereotypical behaviour [2, 3]; wrong diagnoses are often established, e.g. newly detected schizophrenia or bipolar disorders. During this period up to 77% of patients with the above-mentioned symptoms are examined by a psychiatrist. Within a month since the onset of the first symptoms, almost 90% of patients present dyskinesia, seizures, disorders of the sympathetic nervous system (hypotension or hypertension, tachycardia or Bradycardia, hyperthermia, hypersalivation, urine incontinence), consciousness disturbances, catatonia, and even central hypoventilation requiring mechanical support [3]. In our case, instability of the autoimmune system was particularly expressed — severe arrhythmia, tachycardia/bradycardia fluctuations, multiple cardiac arrests in the mechanism of asystole subsiding after a short indirect cardiac massage. According to the literature data, some patients with autoimmune anti-NMDA receptor encephalitis required temporary implantation of a heart stimulator [2]. In order to systematise the characteristic symptoms, in 2008 they were divided into 8 main groups, namely: cognitive; behavioural; memory and speech-related; seizures; motor disorders; loss of consciousness; dysfunction of the autonomic nervous system; and central hypoventilation [5].

The average age of individuals affected by autoimmune anti-NMDA receptor encephalitis is 21 years; however, the literature reports contain cases of patients aged 8 months to 85 years. The most common symptoms in children are neurological disorders (dyskinesia, choreic movements). Memory and behavioural disturbances as well as central hypoventilation are common in adults [3, 5]. About 80% of patients are women and higher incidences are observed among Asians and black individuals [3].

Since the symptoms are weak in terms of characteristics, proper and quick diagnosis seems difficult. MRI of the CNS is not diagnostic in 67% of cases; in the remaining percentage, MRI scans show mild changes, which do not correspond to the severity of symptoms the patients experience [2, 5]. EEG demonstrates abnormalities in the majority of patients (90%) namely, non-specific, slow and disorganised activity of the CNS, periodically accompanied by epileptic activity; however, this activity is not synchronised with the patient’s symptoms and subsides after antiepileptic treatment [2, 5]. Brain biopsy does not lead to accurate diagnosis — its result is generally normal or reveals non-specific inflammatory lesions [2, 3]. Examination of the cerebrospinal fluid is essential for the diagnosis — it shows abnormalities in 80% of cases — lymphocytic pleocytosis, elevated protein concentrations; in 60% of cases, it discloses specific oligoclonal structures, the image being suggestive of inflammatory or immunological origin [1] while the synthesis of anti-NMDA receptor antibodies in CSF has been confirmed in all patients [2]. Antibodies are also simultaneously detected in serum (75%) and can disappear after the onset of immunosuppressive treatment [2, 3]. A tumour (38% of cases), most commonly ovarian teratoma (95%) [5], is found mainly in women aged > 18 years and more commonly in the black race [2]. Low detectability results from the presence of microscopic germinal neoplasms (immature teratomas), which cannot be visualised with the available imaging methods [3]. When an anti-NMDA antibody has been detected, the aim should be to find the tumour underlying the disease (pelvic US, MRI, CT of the entire body, PET, less commonly exploratory
It should be emphasised how important it is to identify the causative factor in the early stage of disease as prognosis after early institution of appropriate treatment is substantially better [6]. The basic therapeutic management is the resection of a tumour (when present), which enables complete recovery or at least accelerates the improvement of the patient’s condition immediately after first-line immunosuppressive treatment has been instituted (80% of patients) [1, 2]. In cases when the above therapy (i.v. glucocorticoids in high doses, plasmapheresis, immunoglobulins) does not cause instant improvement, second-line immunotherapy (cyclophosphamide, rituximab) most commonly results in the desired effects and the subsidence of symptoms (65% of patients) [2, 5]. No protocol regarding the sequence of application of the above-mentioned therapy (both first- and second-line) has been defined; moreover, the efficacy of the use of individual drugs one after another, or simultaneously, has not been proven [5]. Beside the early institution of treatment, the factors improving prognosis include mild severity of symptoms within the first 4 weeks after their onset and a lack of necessary ICU treatment [5]. In 2003, data published in the literature demonstrated that 12% of patients develop recurrences within 24 months, yet in 67% of them, the symptoms are less severe; furthermore, recurrences are more commonly observed in patients undergoing second-line immunotherapy. Tumour removal and immunotherapy substantially improve the neurological conditions of patients in 81% of cases [5]; despite the severity of symptoms, autoimmune anti-NMDA receptor encephalitis is found to have better prognosis for recovery than almost all other paraneoplastic encephalitis cases [1]. Patients respond well to therapies, especially immunosuppressive treatment, although complete recovery can take 18–24 months or longer [5]. The average hospitalisation time is 2.5 months [8]. Recuperation is slow and patients often need additional psychological, occupational and speech therapy. Nevertheless, some patients experience cognitive or motor disorders for a long time [3] and proper social and executive behavioural patterns are the last to return [2]; therefore, the process of complete recovery is longer. Moreover, a lack of recall of the entire disease-related period characteristic of patients who were cured has been demonstrated [8]. However, not all cases end well; the mortality is 7%, and patients die most commonly during the ICU stay. The implicated causes are infections, respiratory failure, sudden cardiac arrest or treatment-resistant status epilepticus [2]. In 2013, the case of a 30-year-old patient with autoimmune encephalitis and the presence of anti-NMDA receptor antibodies was described; the patient was administered the longest active treatment described without improvement. Despite the removal of a teratoma and multiple cycles of first- and second-line immunosuppressive therapy, the level of antibodies in CSF and serum remained significantly elevated. Regrettably, the patient died after 25 months of hospitalisation [9].

**SUMMARY**

The description of this disease is to draw attention to a rare cause of autoimmune encephalitis, whose earlier diagnosis is likely to lead to complete recovery. Special attention should be paid to younger women demonstrating atypical clinical CNS symptoms without any changes detectable during imaging examinations; in such cases, the diagnostic procedures should be focused on finding a tumour in the abdominal cavity.

Until 2014, 577 cases were noted worldwide [5]. The majority of cases diagnosed earlier and those of milder courses are curable. The most common causes of death of those patients are complications typically developing in patients treated in ICUs. The efficacy of treatment is affected by quick diagnosis, the severity of disease, the early institution of treatment and the proper management of intensive therapy-associated complications. Further studies should formulate the best option and duration of immunosuppressive treatment and focus on the role of prodromal symptoms suggestive of inflammatory response and on molecular mechanisms responsible for decreased numbers of NMDA receptors [8].

Moreover, a book written by Susannah Cahalan from New York, entitled *Brain on Fire; My Month of Madness* is noteworthy as it helps the reader to understand the affected mind in such cases.

**ACKNOWLEDGEMENTS**

2. Conflict of interest: none.

**References:**


Corresponding author:
Rafał Wójtowicz, MD
Department of Anaesthesiology and Intensive Care
Central Teaching Hospital in Warsaw
Ministry of Interior and Administration (Mi&A)
ul. Wołoska 137, 02–507 Warszawa, Poland
e-mail: rafałwojtowicz1@wp.pl

Received: 6.12.2016
Accepted: 17.02.2018