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

Rafał Wójtowicz, Magdalena Krawiec, Piotr Orlicz
Klinika Anestezjologii i Intensywnej Terapii Centralnego Szpitala Klinicznego MSWiA w Warszawie

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SUMMARY

The aim of this article is to review the current state of knowledge about anti-N-methyl-D-aspartate receptor encephalitis associated with a neoplastic process, including description of patients, diagnostic process and treatment. The disease concerns mainly young women and correlates with ovarian teratoma. The greatest challenges are associated with difficulties in making a proper diagnosis ensuing from the rarity of this syndrome, the period from the onset of symptoms to treatment implementation and appropriate management of intensive care complications. There are only a few articles that describe severe, complicated cases of this type of encephalitis, where intensive care was needed.

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

Address for correspondence: lek. Rafał Wójtowicz
Klinika Anestezjologii i Intensywnej Terapii Centralny Szpital Kliniczny Ministerstwa Spraw Wewnętrznych i Administracji
ul. Wołoska 137, 02-507 Warszawa
tel. (22) 508 14 50, fax (22) 508 14 58
e-mail: rafalwojtowicz1@wp.pl

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INTRODUCTION

Autoimmune anti-N-methyl-D-aspartate receptor encephalitis was identified in 2007 (1). It is rare encephalitis (only 4%) (2) of the limbic type and is typically diagnosed in young females with paraneoplastic teratomas (3).

Cerebral NMDA receptor blockade leads to characteristic symptoms. GABA neuron inactivation results in psychotic disorders, involuntary movements, fasciculations and nystagmus. Moreover, by affecting the respiratory center in the brainstem, it can cause respiratory disorders requiring mechanical ventilation. Other symptoms, such as sialorrhea, arrhythmias or arterial hypertension, result from the influence on the autonomous nervous system. NMDA receptor disorders are functional in nature and are mostly reversible. That is why proper diagnosis and prompt treatment, involving tumor removal and immunotherapy, may bring positive therapeutic outcomes (4). Approximately 75% of patients with autoimmune anti-NMDA receptor encephalitis have recovered completely or the disease has left only slight consequences. However, it was fatal in 7% of cases and has led to severe deficits in the remaining patients (2,5).

CASE PRESENTATION

A 23-year-old patient, who had previously been generally healthy, was admitted to the Hospital for Infectious Diseases in Warsaw on March 2 2016 due to headache with fever up to 39°C that had been persisting for 48 hours with consciousness disorders, vomiting and photophobia. The patient had complained about headache and malaise 3 days before the onset of fever and reported recent cold. Conventional computed tomography, contrast-enhanced computed tomography and magnetic resonance imaging (MRI), conducted at admission, showed no abnormalities. The examination of

the cerebrospinal fluid revealed increased cytosis of 200/uL (normal range 0–5) and elevated protein level (91.2 mg/dl; normal range 20–40). Other abnormal findings were: increased serum procalcitonin level 0.04 ng/ml, WBC 6.86x10/l (the family interview revealed congenital tendency to leukopenia), HGB 12.8 g/dl and PLT 154 thousand/l. Viral meningitis was suspected. Antibacterial and antiviral treatment was implemented despite unconfirmed etiological agent. Consciousness disorders exacerbated in the next several days of treatment; psychomotor agitation, confusion and anxiety increased. On day 5 of treatment, acute respiratory failure developed. The patient was intubated and transferred to the Intensive Care Unit (ICU). At admission to the ICU, the patient's state was very serious: GCS (*Glasgow Coma Score*) 9, respiratorily inefficient, ventilated mechanically. The targeted therapy against probable pathogens inducing meningoencephalitis was continued. At the same time, extended diagnostic process of the central nervous system pathology was implemented due to the atypical course of the disease. During the whole hospitalization, intensive sialorrhea and increased motor functions persisted despite very high doses of sedatives. After 14 days of mechanical ventilation, tracheotomy was performed. Due to still unconfirmed etiological agent of CNS infection and atypical picture of the disease, unusual causes of meningoencephalitis were sought for. The patient was tested for serum anti-NMDA antibodies with a positive result. Autoimmune anti-NMDA receptor encephalitis was identified. At the same time, an abdominal ultrasound scan (US) revealed a tumor in the region of the left uterine adnexa. In order to broaden the diagnostic process and treat the patient in a multiprofile center, she was transferred to the Intensive Care Unit of the Central Clinical Hospital of the Ministry of Internal Affairs and Administration on April 7 2016.

At admission to our center, the patient's state was very serious. She was unconscious, under deep sedation, unresponsive to stimuli, with lower muscle tone and moderately wide reactive pupils, the left being wider than the right. Myoclonic facial seizures persisted despite continuous infusion of valproic acid. Intensive sialorrhea required continuous suction. The patient was respiratorily inefficient, mechanically ventilated, but cardiovascularly stable. On the second day of hospitalization, she was consulted by a gynecologist. A transvaginal US confirmed the presence of a tumor of the left adnexa. The patient was deemed eligible for its laparoscopic resection. The histopathological examination revealed *teratoma immaturum* which, apart from elements of a dermoid cyst, also contained foci of bone, glial and mature glandular tissues as well as single and slight foci of neuroglia (the largest reaching 2 mm in diameter). For the next several days of treatment, the patient was relatively hemodynamically stable with a tendency to higher pressure and tachyarrhythmia. There were several episodes of heart rate disorders including asystole, which regressed after a short external cardiac massage. Moreover, considerable respiratory hyperactivity persisted; even slight manipulations within the tracheostomy tube led to profound bradycardia. Since admission, hyperthermia had persisted despite the lack of laboratory and clinical evidence of infection, probably of the central nature.

After surgery, a medical conference with a neurologist, nephrologist and gynecologist decided about the implementation of plasmapheresis in order to accelerate anti-NMDA receptor antibody elimination. Five plasmapheresis treatments were conducted in the dialysis unit (day 5, 7, 9, 12 and 14 of hospital stay). Subsequently, the patient was administered immunoglobulins (5 doses of nonspecific human immunoglobulin, each at the dose of 0.5 g/kg of the body weight on day 17, 18, 19, 20 and 21 of hospitalization). Initially, the patient presented intensive psychomotor agitation, myocloni and seizures that were difficult to manage despite a number of combinations of sedatives and antiepileptic agents. Finally, the reduction of the number and intensity of myocloni was obtained upon administration of tetrabenazine combined with quetiapine and baclofen (due to increased muscle tone). During intensive psychomotor agitation, the patient underwent numerous EEG examinations, which failed to unequivocally confirm the epileptic activity in the brain; such activity was noted in only one examination.

On day 20 of hospitalization, the patient developed severe sepsis caused by *Acinetobacter baumannii* and profound leukopenia up to 0.15x10/l with 0% of neutrophils. Targeted antibiotic therapy was administered and filgrastim (granulocyte colony-stimulating factor) was started. This improved the general state of the patient, induced an increase in the number of neutrophils and normalized infection parameters.

On day 29 of treatment, during another medical conference (anesthesiologist, neurolo-

gist, oncologist and nephrologist), a decision was made to start immunosuppressive treatment. When Ethics Committee approval had been obtained, the patient was administered 1000 mg of cyclophosphamide with a mucolytic agent (mesna) and methylprednisolone at a dose of 50 mg (day 37 of treatment). On day 38, 45 and 52, the patient was administered rituximab (a mouse-human anti-CD20 monoclonal antibody) at a dose of 500 mg. The last 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.* Broad-spectrum antibiotic therapy was administered followed by targeted therapy in accordance with microbiological culture results, thus obtaining an improvement of the patient's state and a decrease in inflammatory parameters.

On day 72 of hospitalization, the patient's condition was complicated by infective endocarditis (IE) with vegetation on the mitral valve lateral cusp. Targeted antibiotic therapy was started and continued for 4 weeks. The course of IE was monitored ultrasonographically. After IE, echocardiography presents persisting moderate tricuspid insufficiency, the wave is located posteriorly with no signs of pulmonary hypertension, cardiac cavity dilation or venous stasis. On day 106, antibiotics were discontinued, and on day 115 anti-fungal treatment was stopped.

Up to day 33 of hospitalization, the patient was unconscious with preserved response to stimuli and no logical contact. Gradually, the neurological condition improved. Consciousness returned, sialorrhea regressed and the tendency to hyperthermia decreased. Psychomotor agitation and involuntary movements within the face and extremities regressed gradually. The patient was weaned from mechanical ventilation. She was breathing spontaneously with oxygen supplementation through the tracheostomy tube. On about day 80 of hospitalization, it was possible to establish simple contact with the patient. She gradually started following simple commands and looking at the speaking person. The contact was becoming more and more logical. On day 90 of hospitalization, after releasing tracheostomy tube cuff, the patient tried to utter single words. The tube was removed on day 105. Intensive neurological speech rehabilitation was started. Natural oral nutrition was attempted. During the whole hospitalization, intensive physical rehabilitation was conducted. The patient's neurological condition was improving over the following days. Ultimately, she was conscious, maintained logical verbal contact, answered questioned and solved psychological tests. Memories from before becoming ill were well-preserved, but the patient had problems with short-term memory concerning current events. She read books eagerly, but could not remember what she had read the day before. However, she was able to remember the PIN code for her cell phone which had not been used for 4 months. She was periodically agitated. Also, depressed mood was observed despite antidepressant treatment. The patient developed insomnia. As her neurological state was improving, the physical rehabilitation was intensified. The patient was gradually verticalized at her bed until she began walking with physiotherapist's assistance. After a month of leaving the Intensive Care Unit, she could walk on her own. The patient was consulted by a neurologist, psychiatrist, psychologist and neuro-speech therapist on numerous occasions.

During inpatient treatment, the levels of glutamine anti-NMDA receptor antibodies in both blood and cerebrospinal fluid were controlled. Initially, they were present in the following dilutions: 1:10, 1:100 and 1:1000 (strong reaction). After ovarian teratoma removal and 5 cycles of plasmapheresis, the serum antibody levels decreased. Antibodies were present in 1:10 and 1:100 dilution (strong reaction), but were undetectable in 1:1000 dilution. This level persisted in a follow-up test performed one month after immunosuppressive treatment. In the second month after this therapy, anti-NMDA receptor antibodies were still detectable in 1:10 dilution (strong reaction); weak positive reaction was seen in 1:100 dilution and no reaction in 1:1000 dilution. As the literature states, the antibody level is not directly correlated with patient's clinical state and can persist high long after recovery, more frequently in the cerebrospinal fluid than in serum (2). Another test conducted in the second month after discharge from the ICU showed no changes: the serum level was still high.

The result of blood and cerebrospinal fluid flow cytometry seems to be equally reliable. Before immunosuppressive treatment, the test showed a cytometric picture with prevailing T CD4+/ HLA DR+ lymphocyte and macrophage population with single eosinophilic granulocytes, as it is seen in autoimmune encephalitis, which was consistent with the clinical diagnosis. In the second month after immunothe-

rapy, follow-up cytometry demonstrated no B cells of CD20+/CD19+ phenotype.

On day 85 of treatment, positron emission tomography – computed tomography (PET-CT) was performed in order to assess the radicality of treatment and CNS metabolic activity. The examination showed no changes of the active proliferative process, but revealed symmetrically enhanced tracer accumulation in the basal nuclei and cortex. Moreover, increased tracer accumulation was observed at the interface of the superior temporal gyrus and insula (less visible in the delayed assessment). On day 120, bone marrow punch biopsy was carried out due to recurring leukopenia. It was found that the probable cause is an autoimmune reaction.

On August 10 2016, after 160 days of hospitalization, including 127 days of treatment, the patient, at her parents' request, was discharged in a stable overall state, conscious with fully preserved logical contact, respiratorily and cardiovascularly stable. She was ordered treatment continuation, 24h care with monitoring of vital signs, intensive rehabilitation as well as psychiatric and hematologic consultation. At home settings, the patient's state is gradually improving. Sleeplessness is regressing and short-term memory is improving. The patient is receiving intensive physical rehabilitation and speech therapy. She is becoming self-sufficient; prepares meals on her own, exercises eagerly and learns how to drive and speak English. She is planning to return to university. She still has no recollection of the whole period of the illness.

DISCUSSION

Limbic encephalitis, which includes autoimmune encephalitis associated with the presence of anti-NMDA receptor antibodies, was first described in 1960 by Brierley et al. as a paraneoplastic encephalitis involving the limbic region (hippocampus, thalamus, hypothalamus, amygdalae) connected with neoplasms of the lungs, breast, ovary, uterus, stomach, kidneys, urinary bladder and large intestine (6). It was suggested that encephalitis could be caused by autoaggression against limbic system antigens. In 2001, two cases of limbic encephalitis associated with potassium channel antibodies were reported, and in 2003, an NR2 subunit of anti-NMDA receptor antibody was found in the brain of some patients with acute encephalitis, including that of the limbic type. The role of inflammatory and immunological processes in encephalitis has become of interest to various medical circles (6). This disease has been identified in 577 patients worldwide (5).

In 2005, a syndrome of psychiatric symptoms with consciousness disorders and central hypoventilation was reported in 4 young women with ovarian teratoma (7). The year 2007 when Dalmau et al. identified this syndrome as autoimmune anti-NMDA receptor encephalitis brought a breakthrough (1). NMDA receptors are located in the hippocampus and forebrain. It is a type of receptor for glutamate which is selectively activated by N-methyl-D-aspartate (NMDA) acid. It is an ionotropic receptor conducting sodium (Na^+), potassium (K^+) and calcium (Ca^{2+}) cations. Apart from glutamate, its activation requires binding of glycine and serine. Ovarian teratoma is the most common cancer that induces the formation of anti-NMDA receptor antibodies due to the presence of various types of tissues in the tumor. In our patient, this was caused by the presence of neuroglial cells. The produced antibodies block the NR1 subunit of NMDA receptor in the brain, thereby inducing its inflammation, which manifests mostly with disorders of memory, behavior and consciousness as well as seizures. This atypical picture (with prevailing psychiatric symptoms), patient profile (relatively young women between the second and fifth decades of life), normal or completely atypical MRI image of the brain and the presence of a benign ovarian tumor makes autoimmune anti-NMDA receptor encephalitis unique among all types of paraneoplastic encephalitis (1).

The fact that the disease occurs in previously healthy, young women with a sudden onset of emotional disorders is typical of autoimmune anti-NMDA receptor encephalitis (3). Its course can be divided into several stages of illness and recovery. Approximately 70% of patients present prodromal symptoms, such as headache, nausea, diarrhea, fatigue, fever and signs of upper respiratory tract infection. Within the next several days, psychiatric symptoms, such as mania, paranoia and anxiety, develop. More rarely, memory disorders or stereotypical behaviors are observed (2,3). Frequently, the diagnoses are incorrect, e.g. newly diagnosed schizophrenia or bipolar disorder. Up to 77% of patients with these symptoms receive psychiatric consultation. Within a month of the onset, almost 90% of patients present dyskinesias, seizures, sympathetic nervous system disorders (hyper- or hypotension, tachy- or bradycardia, hyperthermia, excessive salivation,

urinary incontinence), consciousness disorders, catatonia and central hypoventilation requiring mechanical ventilation (3). Autonomous system instability was particularly expressed in our patient. She presented severe arrhythmias, fluctuations between tachy- and bradycardia, including several episodes of cardiac arrest (asystole) that regressed upon several minutes of indirect cardiac massage. Literature data indicate that certain patients with anti-NMDA receptor encephalitis require temporary pacemaker implantation (2). In 2013, in order to systematize typical symptoms, they were categorized into 8 main groups: cognition, behavior, memory and speech disorders, seizures, movement disorders, loss of consciousness, autonomic dysfunction and central hypoventilation (5).

The mean age of patients with anti-NMDA receptor encephalitis is 21 years, but the literature reports cases at the age of 8 months to 85 years. The most common symptoms in children include neurological disorders (dyskinesias, choreatic movements), whereas memory and behavior disorders as well as central hypoventilation are the most common signs in adults (5,3). Approximately 80% of patients are females, and the syndrome more frequently develops in individuals of Asian and black races (3).

Taking into account poorly specific symptoms, appropriate and prompt diagnosis seems difficult. Central nervous system MRI is non-diagnostic in 67% of cases. The remaining patients present benign changes that do not reflect the severity of the clinical symptoms (2,5). EEG shows abnormalities in most patients (90%): non-specific, slow and disorganized CNS activity with periodical seizures. However, this activity is not synchronized with the clinical symptoms and does not subside upon administration of antiepileptic drugs (2,5). Brain biopsy does not lead to the correct diagnosis; the result is usually normal or indicates non-specific inflammatory changes (2,3). The cerebrospinal fluid analysis is of the greatest diagnostic significance. It shows abnormalities in 80% of cases. The findings include: lymphocytic pleocytosis, elevated protein concentrations and specific oligoclonal structures in 60% of cases; the picture suggests inflammatory of immunologic background of the disease (1). Additionally, all patients present anti-NMDA receptor antibody synthesis in the cerebrospinal fluid (2). Antibodies are also detected in the serum (75%), but they might disappear upon implementation of immunosuppressive treatment (2,3). Tumors (38% of cases), usually ovarian teratoma (94%) (5), are found mostly in patients older than 18 years of age and predominantly in black women (2). Low tumor detectability results from the presence of microscopic germ-cell neoplasms (immature teratomas), which are impossible to detect with currently used imaging technology (3). If anti-NMDA receptor antibodies are detected, a tumor should be sought for as the underlying cause of the disease (pelvic US, MRI, whole-body CT, PET scan, more rarely exploratory laparoscopy) (3). The tumor contains cerebral tissue in nearly 100% of cases (5).

The fact that early identification of the causative factor is critical is undisputed since prognosis improves considerably when appropriate treatment is implemented early (6). The principal management involves tumor removal (if it is present), which enables complete recovery, or at least accelerates improvement, soon after implementation of first-line immunosuppression (80% of patients) (1,2). If first-line immunosuppression (high doses of intravenous steroids, plasmapheresis, immunoglobulins) does not result in instantaneous improvement, second-line immunosuppression (cyclophosphamide and rituximab) usually brings desired effects and regression of symptoms (65% of patients) (2,5). There is no predefined protocol concerning the order within both first- and second-line therapy. Moreover, the efficacy of individual drugs used in a given order or combination has not been proven either (5). Apart from early therapy, factors that improve prognosis include benign symptoms within the first 4 weeks after the onset and no necessity of treatment in an intensive care unit (5). In 2013, a study was published which shows that 12% of patients develop a relapse within 24 months, but the symptoms are milder in 67% cases; relapses more rarely occur in patients treated with second-line therapy. Tumor removal and immunotherapy lead to considerable improvement of the neurological condition in 81% of patients (5) and, despite the severity of symptoms, anti-NMDA receptor encephalitis carries better prognosis than almost all other types of paraneoplastic encephalitis (1). Patients respond well to introduced treatment, particularly immunotherapy, although full recovery may last 18–24 months or even longer (5). The mean time of inpatient treatment is 2.5 months (8). Convalescence is slow and patients frequently require psychological, group and speech therapy. Despite this, some patients struggle with co-

gnitive and movement disorders for a long time (3) and proper social behavior and executive functions are the last to return (2), which prolongs the process of complete convalescence. Also, persistent lack of memory concerning the entire period of being ill is typical of patients after autoimmune anti-NMDA receptor encephalitis (8). However, the end of the disease is not always positive. The mortality amounts to 7% (5), with death usually occurring during treatment in the intensive care unit. Among causes, authors enumerate infection, respiratory distress, sudden cardiac arrest and refractory status epilepticus (2). In 2013, a case of a 30-year-old patient with autoimmune anti-NMDA receptor encephalitis was reported who underwent so far the longest active treatment without improvement. Despite teratoma removal and numerous cycles of first- and second-line immunosuppression, significantly elevated antibody levels persisted both in the serum and cerebrospinal fluid, which was a severe prognostic factor. The patient died after 25 months of hospitalization (9).

CONCLUSION

The aim of the description of this disease entity was to draw attention to a rare cause of autoimmune encephalitis which, when detected early, makes it possible to obtain full recovery. Particular attention should be paid to young women who manifest atypical clinical signs within the central nervous system without tangible changes in imaging. This should prompt the search for a tumor in the abdominal cavity.

Up to 2014, 577 cases of this disease had been reported worldwide (5). Milder, early detected cases are mostly curable. The most common causes of death are complications of intensive care. Treatment efficacy is affected by the promptness of diagnosis, severity of the course, early treatment implementation and proper management of intensive care complications. Future studies should clarify the best type and length of immunotherapy as well as pay greater attention to the role of prodromal symptoms, which suggest the inflammatory response, and to the molecular mechanisms involved in decreasing the number of NMDA receptors (8).

The book entitled "Brain on Fire; My Month of Madness," written by a journalist from New York, Susannah Cahalan, who had autoimmune encephalitis, is an interesting reading that helps understand what happens in the mind of the patient with this disease. The book has also been translated into Polish.

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