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Acute psychosis due to non-paraneoplastic anti-NMDA-receptor encephalitis in a teenage girl: Case report

Sandra Kramina,[1] Laura Kevere,[2] Nikita Bezborodovs,[2] Santa Purvina,[3] Guntis Rozentals,[4] Jurgis Strautmanis,[4] and Zane Viksna[4]

[1]Riga Stradins University, Riga, Latvia, [2]Child Psychiatry Clinic, Children's Clinical University Hospital, Riga, Latvia, [3]Department of Internal Diseases, Riga Stradins University, Riga, Latvia, [4]Child Neurology and Neurosurgery Clinic, Children's Clinical University Hospital, Riga, Latvia

Abstract: Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a disease occurring when antibodies produced by the body's own immune system attack NMDA-type glutamate receptors in the brain. Most anti-NMDAR encephalitis cases are associated with paraneoplastic syndrome. We analyze the case of a 15-year-old girl who was hospitalized in a child psychiatry clinic in Riga, Latvia, with de novo acute polymorphic psychotic disorder gradually progressing to a catatonic state. The patient received antipsychotic and electroconvulsive therapy with no beneficial effect. The council of doctors discussed differential diagnoses of schizophrenia-induced catatonia and the autoimmune limbic encephalitis-induced catatonic condition. When the diagnosis of anti-NMDAR autoimmune encephalitis was finally confirmed by repeated immunological assays (specific immunoglobulin [Ig] G and IgM in her blood serum and cerebrospinal fluid), and a paraneoplastic process was ruled out, she was started on immunomodulating therapy (methylprednisolone, Ig, plasmapheresis, rituximab), which changed the course of her disease. On immunomodulating treatment, her physical and mental health have gradually improved to almost complete reconvalescence. Psychiatrists should consider anti-NMDAR encephalitis as a differential diagnosis in first-episode psychosis patients presenting with disorientation, disturbed consciousness, pronounced cognitive deficits, movement disorder, dysautonomia, or rapid deterioration, and test for specific IgG NR1 autoantibodies, even if there are no specific findings on routine neuroimaging, electroencephalography (EEG), or cerebrospinal fluid tests.

Keywords: acute psychosis; anti-*N*-methyl-D-aspartate receptor (anti-NMDAR); non-paraneoplastic encephalitis

Correspondence: Dr. Laura Kevere, Children's Clinical University Hospital, Child Psychiatry Clinic, Juglas Str. 20, Rīga, LV-1079, Latvia. Email: kevere@gmail.com

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Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a severe autoimmune disease. It is the second most common cause of encephalitis among children (Lancaster, Martinez-Hernandez, & Dalmau, 2011) and can lead to irreversible disability or even death. It is a treatment-responsive encephalitis, associated with anti-NMDAR antibodies, typically presenting with marked neuropsychiatric symptoms (delusional thought contents, perceptual disturbances, disorganized thoughts, anxiety/fear and agitation, paranoid ideation, mood labiality, bizarre behaviors, and personality change), after which epileptic seizures, prolonged respiratory failure, clouded consciousness, and bizarre dyskinesia are frequently observed (Sameshima et al., 2011).

Initially, this disease had been classified as a part of paraneoplastic syndrome (Dalmau et al., 2007), but in pediatric populations, a tumor is most often not found.

This disease mainly affects young people, approximately 30% have been identified up to the age of 18, and it is more common among women than men, possibly due to its co-occurrence with ovarian teratoma, which is a serious and potentially fatal pathology occurring in young women. Unfortunately, in many countries, this association is

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relatively unknown or unreported among gynecologists (Acién, Acién, Ruiz-Maciá, & Martín-Estefanía, 2014).

The aim of this article is to analyze the first case of anti-NMDAR encephalitis registered in child psychiatry practice in Latvia, highlighting the diagnostic complexities and therapeutic options.

Case presentation

A 15-year-old girl was first admitted to a child psychiatry clinic in Riga, Latvia, with symptoms of acute psychosis in April 2014. Her mother had noticed some changes in her behavior 6 months prior to hospitalization—she became more moody, absentminded, started having problems with concentrating at school, and became more conflicting at home. Gradually the behavioral and cognitive problems worsened, she became obsessive about cleanliness, socially withdrawn, started spending long hours at home sitting in one pose, and her speech became at times illegible. A week prior to hospitalization, these symptoms progressed to the point when she could not respond to a question or finish a sentence, and started having episodes of confusion, unresponsiveness, and extreme fear. At this point, her mother decided to seek medical help.

Her life history showed that she was an only child. Her mother had a prolonged period of depression after the father left the family while she was still pregnant. Her father, although not being formally diagnosed, had a history of paranoia—he was afraid of being under surveillance by intelligence services, and feared being poisoned or killed. The girl was born in complicated labor; she suffered postpartum aspiration pneumonia, and was treated in the intensive care unit for 2 weeks. From a very early age, she had almost no hearing in her right ear. From the age of 5, she had frequent headaches, vomiting, and was investigated for migraine and metabolic disorders, but none of the diagnoses were confirmed. Due to her headaches, she underwent two consecutive magnetic resonance imaging (MRI) examinations at ages 10 and 11. Both showed multiple small hyperintense foci in both hemispheres, probably as a result of perinatal hypoxic ischemic damage. The foci showed no dynamic over a year.

Upon admission to the psychiatric clinic, the girl's mental state was evaluated as acutely psychotic. She appeared fearful, and the staff had an impression from the way that she behaved that she had auditory hallucinations. In the hospital, the patient had psychomotor agitation and was not available for productive contact; she did not answer questions and kept repeating stereotypically the same words. However, because of the impaired contact, no first-person account of perceptual disturbances or delusional thought content could be elicited. Antipsychotic (haloperidol, olanzapine) and anxiolytic treatment was started, but despite that, her condition continued deteriorating, and she became progressively more agitated. Electroencephalography (EEG) and MRI were conducted to exclude organic pathology; the EEG showed no paroxysmal activity, and the results of the MRI were similar to the ones conducted at ages 10 and 11 (multiple small foci due to perinatal hypoxic ischemic damage). Meanwhile, her condition continued progressing to a catatonic state—she refused food and liquids, periods of stupor interchanging with periods of psychomotor agitation. Twenty days after her initial admission, she was transferred to an intensive care unit (ICU), where she was put into a medically induced sleep. While in the ICU, she continued to receive haloperidol and midazolam, with no beneficial effect. Due to her unresponsiveness to drug therapies, it was decided to try electroconvulsive therapy, and she received two procedures without positive dynamics in her state. At this point she also started developing neurological signs—she bit her right cheek, she always extended her right arm when sitting up—which could have indicated an involvement of the left hemisphere in some yet unknown disease process. Later she started having difficulty swallowing, first when eating solid food, later on also swallowing liquids, as well as other signs of an autonomic dysregulation.

Due to the co-occurrence of treatment-resistant catatonic symptomatology with neurological signs and dysautonomia, a differential diagnosis of autoimmune encephalitis was established. A lumbar puncture was carried out, which showed normal protein and glucose, but an elevated white blood cell (mostly lymphocytes) count, and it was decided to start immunomodulating treatment. She was started on intravenous methylprednisolone, immunoglobulin (Ig) infusions, and received three consecutive plasma exchange treatments, as well as anticonvulsant medication. One month after her initial admission, the immunological analyses of her blood and cerebrospinal fluid (CSF) returned positive for specific anti-glutamate receptor (NMDA type) antibodies (IgA, IgG and IgM) and the diagnosis of autoimmune anti-NMDAR encephalitis was confirmed. Immunoassays were performed using the EUROIMMUN slides (indirect immunofluorescence method) in the Winfried Stocker Laboratory, Lubeck, Germany. The IgG antibody titers in the serum and CSF

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samples were 1:320 and 1:32, respectively. The patient then received a thorough workup for possible cancer, including serological investigations, MRI of the thoracic, abdominal and pelvic cavity organs, repeated brain scans, all with no evidence of malignancy.

While receiving her third plasma exchange procedure, she developed pulmonary artery thromboembolism, went into cardiogenic shock, and received two successful cardiopulmonary reanimations. An acute angiography and thrombolysis were preformed. Ten days after her diagnosis was confirmed by immunological assay and an extended council, it was authorized to switch her to the second-line treatments, as she was not responding to the first line of immunomodulating therapy. She was started on intravenous rituximab once a week (one course in 4 weeks), and received four courses. She also received cyclophosphamide and sulfamethoxazole/trimetoprim, as well as anticonvulsants, antibiotics, antihypertensive medication, and blood thinners.

Two weeks into rituximab therapy, her state slowly started improving: She started breathing spontaneously, hyperkinesias reduced, and she gradually started eating and drinking without a nasogastral tube. However, she had pronounced cognitive impairment, psychiatric symptoms (impulsivity, aggression towards others, speech disorder), and frequent episodes of psychomotor agitation.

She was discharged from the hospital and was treated on an outpatient basis. One month after discharge, she could read, and her memory had substantially improved, but she was still weak and had substantial psychiatric symptoms (erratic behavior, episodes of agitation, selective mutism, sleep disturbances). She also experienced side-effects of treatment: increased appetite and signs of Cushing's syndrome. In addition to the chemotherapy with rituximab and glucocorticoids, she also continued to receive anticonvulsants (lamotrigine, clonazepam).

Three months after her diagnosis was confirmed, her blood serum was sent for a repeated immunological analysis, and this time the IgA and IgM anti-NMDAR antibodies were negative, while she still tested positive for IgG antibodies.

In August 2014, the chemotherapy courses were stopped, and from December 2014 she no longer received any anticonvulsant or other psychotropic medication.

In March 2015, a year after her hospitalization, she was inspected by a child and adolescent psychiatrist. She had completely returned to her normal routine. She was fully independent in her everyday activities (bathing, dressing, walking a dog, reading, etc.), but still needed her mother's help in some aspects of everyday life, for example, she requested that her mother put a sticker on the sink indicating the hot and cold water, she also needed the food in the refrigerator to be labeled with stickers, and used written reminders of the location of different objects at home. Her mother related that she was still experiencing rapid mood swings, but she no longer had episodes of agitation or aggression. Sometimes she still had difficulties in making decisions (which was not a problem before she became ill), and she would occasionally mix left and right sides. She had no motor deficits, but experienced complete amnesia of the period of hospital treatment. She had returned to school and had good grades.

Discussion

Anti-NMDAR encephalitis is a form of autoimmune encephalitis associated with antibodies against the NR1 subunits of NMDARs. Despite ample documentation for patients with NMDAR encephalitis of newly onset and acute prominent psychotic syndromes, studies are still deficient for differential diagnosis and treatment of anti-NMDAR encephalitis cases that follow a long-term diagnostic history of functional psychotic disorders (Huang et al., 2015). The typical presentation of anti-NMDAR encephalitis includes acute behavioral and cognitive disorder, movement disorder, memory deficits, speech impairment, seizures, reduced consciousness, dysfunction of the autonomic nervous system, and central hypoventilation. It is known that bigger reduction in the concentration of specific antibodies in the cerebrospinal fluid correlates with better clinical outcome (Gresa-Arribas et al., 2014). Teenagers and adults more often have memory deficits, autonomic dysfunction, and central hypoventilation, whereas children who are younger than 12 more often have behavioral and cognitive disorders, spontaneous movements, speech disorder, ataxia, and paresis. Similar to the growing number of cases of anti-NMDAR encephalitis not connected to paraneoplastic syndrome published in recent years, our patient also did not have an identifiable tumor that could have triggered the autoimmune process (Dalmau, Lancaster, Martinez-Hernandez, Rosenfeld, & Balice-Gordon, 2011; Zandi et al., 2014).

Like many of the described cases, our patient's disease also started with a flu-like symptom prodrome that was followed by psychiatric symptoms (personality change, anxiety, auditory hallucinations, compulsive ideation) gradually progressing to a catatonic state (with mutism, negativism, and

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psychomotor agitation), and later followed by marked cognitive decline, movement disorder (dyskinesias), autonomic dysregulation, and other neurological signs (Florance et al., 2009; Gable et al., 2009; Kayser & Dalmau, 2011; Titulaer et al., 2012).

Pleocytosis of the cerebrospinal fluid with or without elevated protein or oligoclonal cell band has been described in almost all known cases currently published in the literature (Dalmau et al., 2008; Florance et al., 2009; Titulaer et al., 2012). The MRI findings in patients with anti-NMDAR encephalitis are variable and mostly non-specific (Dalmau et al., 2011; Titulaer et al., 2012), which was also true for our patient.

There is currently no universally accepted treatment protocol for anti-NMDAR encephalitis. The recommended first-line treatment includes corticosteroids, intravenous Ig, plasma exchange, as well as surgical treatment if a tumor is identified (Kruse et al., 2014).

For patients in whom the first-line treatment is ineffective (more often observed among patients with non-paraneoplastic autoimmune encephalitis), the second-line treatment, immunotherapy, is required. The second-line treatment includes rituximab and/or cyclophosphamide, as well as the immunosuppressive agent mycophenolate mofetil, which is recommended for patients with non-paraneoplastic encephalitis for a minimum of 1 year, and periodic screening for ovary teratoma (or other tumor) for a minimum of 2 years after recovery.

Our patient did not respond to the first-line therapy and required the second-line treatment, which fortunately resulted in substantial improvement of her health status.

The literature shows that approximately 75% of patients with anti-NMDAR encephalitis achieve substantial or even full recovery. It has been reported that the clinical recovery period can be from some weeks up to 2 years (Dalmau et al., 2011; Titulaer et al., 2012).

Our patient required a multidisciplinary rehabilitation after her discharge from the hospital, similar to other cases described in the literature (Chapman & Vause, 2011; Florance et al., 2009; Titulaer et al., 2012). She has received regular sessions with a psychologist, speech therapist, and an occupational therapist.

Conclusion

Psychiatrists should consider anti-NMDAR encephalitis as a differential diagnosis in first-episode psychosis patients, especially if the onset of psychotic and behavioral symptoms (anxiety, agitation, bizarre behavior, delusions, and hallucinations) is rapid, and followed by symptoms of disorientation, disturbed consciousness, pronounced cognitive deficits, movement disorder (e.g. dystonia), autonomic disturbance, or rapid deterioration. Clinicians should test for specific IgG NR1 autoantibodies, even if there are no specific findings on routine neuroimaging, EEG, or cerebrospinal fluid tests.

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