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Case Report **Open Access**

Adolescent with acute psychosis due to anti-*N*-methyl-D-aspartate receptor encephalitis: successful recovery

Dovile Jonuskaite[1,2,*], Paulius Kalibatas[1,2], Ruta Praninskiene[1,2], Asta Zalubiene[3], Aurelija Jucaite[4], Rimante Cerkauskiene[1,2]

[1]Children's Hospital, Affiliate of Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania;
[2]Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania;
[3]University Dep. of Child and Adolescent Psychiatry, Republican Vilnius Psychiatry Hospital, Vilnius, Lithuania;
[4]Dep. of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

***Corresponding author:** dovile.jonuskaite@santa.lt

Abstract

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a relatively new autoimmune disorder of the central nervous system. We report the first case of anti-NMDAR autoimmune encephalitis combined with anti-voltage-gated potassium channel (anti-VGKC) antibodies in Lithuania in a 16-year-old girl. The patient was admitted to psychiatry unit because of an acute psychotic episode. She was unsuccessfully treated with antipsychotics, and electroconvulsive therapy was initiated because of her rapidly deteriorating condition. Electroconvulsive therapy improved the patient's condition even before the initiation of immunomodulatory therapy. The abrupt onset, atypical and severe course of psychosis, poor response to antipsychotic treatment, and signs of flu-like prodromal period led to the search of non-psychiatric causes. Although with considerable delay, she was screened for an autoimmune encephalitis. Positive anti-NMDA receptor antibodies were found in the cerebrospinal fluid, but not in serum. In addition, serum was found positive for antinuclear antibodies and anti-VGKC antibodies but negative for CASPR2 and LGI1 antibodies. The girl was treated with intravenous immunoglobulin and methylprednisolone with satisfactory response, although infrequent orofacial movements, emotional lability, and learning deficits remained upon discharge. The reported case suggests that multiple antibodies could be present, and that electroconvulsive therapy may have a role in symptomatic treatment of autoimmune encephalitis.

Keywords: acute psychosis; adolescent; anti-NMDAR encephalitis; anti-VGKC encephalitis

Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a relatively newly discovered disorder with progressive clinical course and attainable treatment efficacy (1,2). The first cases of non-infectious limbic encephalitis of reversible nature associated with ovarian teratoma were reported in a young woman and an adolescent girl in 1997 (3,4). Description of antibodies against synaptic NMDA receptors causing this autoimmune illness soon followed (5). Anti-NMDAR encephalitis has since been observed also in cases without teratoma, in both genders, and in all ages (from eight months to 85 years) (1). Among them, up to 40% of reported cases have occurred under the age of 18 years (1). In infants and young children, the clinical presentation more often starts with neurological symptoms, such as abnormal movements or seizures (6,7). In adolescents, the disease may be more obscure due to initial manifestation of psychiatric symptoms or cognitive dysfunction leading to the delayed therapeutic interventions. If untreated, anti-NMDAR encephalitis can be a devastating disease. However, immunotherapy has shown favorable outcomes in 81% of patients (1). Thus, awareness of anti-NMDAR encephalitis in the differential

diagnosis of acute adolescent psychosis is of great importance.

Encephalitis with anti-voltage-gated potassium channel (anti-VGKC) complex antibodies is a rare condition (7,8). The anti-VGKC antibodies are directed against the VGKC-complex proteins, which include leucine-rich glioma inactivated 1 (LGI1), contactin-associated protein-2 (CASPR2), and other proteins (9). The clinical characteristics of encephalitis, such as seizures, memory loss, sleep disturbance, as well as laboratory findings of hyponatremia, inflammatory cerebrospinal fluid (CSF), temporal lobe abnormalities on magnetic resonance imaging (MRI), and abnormal electroencephalography (EEG) have been previously described (10). A case of autoimmune encephalitis seropositive for NMDAR and VGKC antibodies has been reported; however, the role of multiple antibodies in the clinical course of disease is not well understood (11).

It is extremely important to target both pathogenesis and clinical syndrome of the encephalitis to achieve successful recovery. In case of teratoma-associated anti-NMDAR encephalitis, it is crucial to remove tumor to improve symptoms. Although specific immunotherapy regimens and their long-term outcomes have not been validated, early immunotherapy and a second-line therapy have been associated with fewer relapses (1). The first-line treatment is immunotherapy with corticosteroids, intravenous immunoglobulins, a combination of both, or plasmapheresis (12). There is evidence that therapeutic apheresis is particularly effective in patients with antibodies against neuronal surface structures and treatment outcomes do not correlate with the timing of intervention (13). After unsuccessful or incomplete recovery from the first-line therapy there are several strategies for further treatment. Rituximab has been increasingly reported as a relatively safe and effective drug of choice in pediatric anti-NMDAR encephalitis cases (12). Immunosuppression with cyclophosphamide is a second frequently reported drug of choice (12).

An autoimmune encephalitis is a well described and potentially treatable condition, which requires early recognition and intervention. In many clinical settings first-line treatment initiation usually is based on the clinical diagnosis because awaiting results of serologic studies could delay treatment (12). Therefore, clinical suspicion and awareness of autoimmune condition as a cause of acute psychosis are essential. As antibody-associated autoimmune encephalitis is a relatively new entity in child and adolescent psychiatry there is an urgent need for increased awareness among clinicians dealing with acute psychiatric conditions in children and adolescents. The presented case of autoimmune encephalitis is remarkable because of acute presentation, the effectiveness of electroconvulsive therapy (ECT), positive tests for multiple antibodies against neuronal structures late in the course of the disease, concomitant autoimmune thyroiditis, and favorable outcome despite delayed immunotherapy. The authors believe that this case represents a classical picture of anti-NMDAR encephalitis with common problems arising in a clinical setting.

Clinical case report

A 16-year-old girl was admitted to psychiatry intensive care unit because of the first acute psychotic episode. Over the last year, the girl had been reporting various minor health problems such as fatigue, joint pain, muscle tenderness, oily skin, and constant subfebrile temperature. Mild thyroid hypofunction was found, and the girl was diagnosed with autoimmune thyroiditis and was prescribed L-thyroxin. Subtle changes in the patient's mood, behavior, and cognitive functions preceded a month before the sudden manifestation of psychosis. The girl also reported weight loss of about 4 kg in one month.

On admission, the patient was severely agitated. Vital signs were normal as well as head computed tomographic scan and routine laboratory examinations. Thyroid hormone levels were also normal. She was seronegative for tick-borne encephalitis virus and *Borrelia burgdorferi* (tested IgM and IgG, ELISA). Because of the progression to oneiroid syndrome the patient was put on intravenous haloperidol 2.5 mg/day plus trihexyphenidyl 2 mg/day, which induced extrapyramidal symptoms on the second day of treatment. The patient's condition continued to deteriorate; she became fully disoriented in time and place and had excessive perceptual anomalies with vivid visual and auditory hallucinations. The speech disturbances rapidly progressed to partial mutism and inability to read and write. Episodic posturing, orofacial dyskinesia, stereotypical hand movements, autonomic dysfunction (severe blood pressure fluctuations), and subfebrile temperature were observed. Severe insomnia was resistant to treatment with benzodiazepines and lasted for two weeks. An early onset of extrapyramidal side effects and fully developed positive psychotic symptoms while on haloperidol have led to the therapy change. The patient was prescribed intravenous olanzapine, which was later changed to oral quetiapine, but psychotic symptoms were refractory to the antipsychotic treatment. ECT is not a common choice in the clinical practice of adolescent psychiatry, but in the light of life-threatening catatonia and ineffective treatment with several antipsychotics, the patient was given eight

procedures of ECT. On the fifth week of acute illness the patient's clinical status finally started to improve.

Severe course of psychosis and resistance to antipsychotic therapy warranted further diagnostic evaluation. Autonomic dysfunction, subfebrile temperature, and stereotypies in association with acute psychosis caused the suspicion of autoimmune encephalitis. On the fourth week of illness serum was tested for anti-NMDAR antibodies and found to be negative (test was performed at Gemeinschaftslabor Cottbus, Lübbenau, Germany). Brain MRI (1.5 T) showed no pathologic changes. EEG showed intermittent slow delta-theta wave activity in parietotemporal and centrofrontal regions. Extensive tumor screening (ultrasound of the urogenital system, abdominal and pelvic MRI, and chest computed tomographic scan) was negative.

Further, an immunological examination was performed. It included blood serum measurements for antinuclear, anti-dsDNA, anti-ribosomal P, anti-cardiolipin, and anti-beta2 glycoprotein-I antibodies. Only antinuclear antibodies were found positive (dilution > 1:200, immunofluorescence method, local diagnostic laboratory) and remained positive on repeated testing after three months. On the fourth month of illness serum test was repeated for anti-NMDAR antibodies and was also negative; however, a CSF sample showed positive oligoclonal bands and was found positive for anti-NMDAR antibodies (indirect immunofluorescence at Eurodiagnostica Wieslab, Malmo, Sweden). In addition, blood serum was tested for antibodies against VGKC-complex (including CASPR2 and LGI1) and GABA-b receptors and was found positive for VGKC, with a value of 394 pmol/l for the latter (radioimmunoprecipitation method; the result is considered clinically significant if value is over 300 pmol/l; Eurodiagnostica Wieslab) (Figure 1).

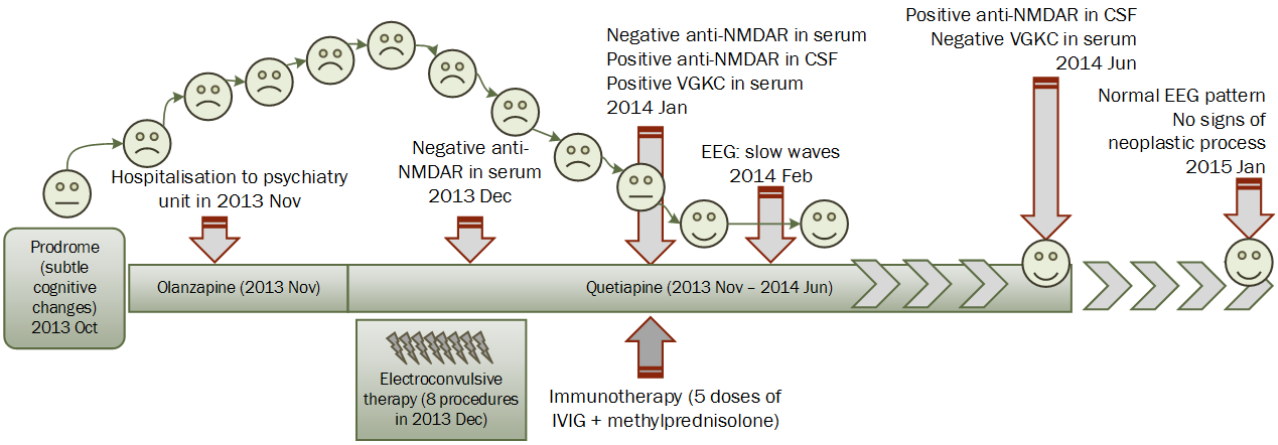

FIGURE 1. Evolution of clinical symptoms and response to treatment. Anti-NMDAR, anti-*N*-methyl-D-aspartate receptor; CSF, cerebrospinal fluid; EEG, electroencephalography; VGKC, voltage-gated potassium channel.

The patient received immunotherapy with intravenous methylprednisolone (five pulses of 1 g daily) and IVIG (five pulses of 0.4 g/kg daily). At that time, the only remaining symptoms were occasional orofacial movements while asleep and mild learning difficulties. The patient continued quetiapine 300 mg/day for several months and was medication free nine months after the manifestation of disease.

NMDAR antibodies in CSF were still positive on the tenth month of disease; however, anti-VGKC antibodies in serum were negative. The patient's mental status, however, remained normal. At follow up after a year, the patient reported mild memory problems. The outcome was categorized as full clinical recovery.

Informed consent of the family was obtained for the case report according to the national and institutional ethical rules.

Discussion

We report the representative case of an adolescent girl with autoimmune encephalitis manifesting with severe acute psychosis that progressed from initial psychiatric symptoms to memory disturbance, dyskinesia, and catatonia. The clinical course, EEG findings, and normal MRI were consistent with published data (6,14,15). Negative anti-NMDAR serum sample results and positive findings in CSF were reported in recent literature, especially early in the disease course (16). Uncommon findings of anti-NMDAR and anti-VGKC in the same patient were

previously described (6), but not in a case of adolescent with an acute psychotic episode. According to current knowledge, positive test for anti-VGKC antibodies without evidence of CASPR2 or LGI1 antibodies production is of doubtful clinical relevance (8). Therefore, the authors believe that the most likely explanation of clinical symptoms and findings in the reported case is anti-NMDAR encephalitis with false positive anti-VGKC antibodies. Although the reported case started to improve even before the immunotherapy, physicians made the rather difficult decision to introduce treatment. This was based on the increasing knowledge that anti-NMDAR encephalitis tends to relapse more frequently if treatment is incomplete during the manifestation of illness and anti-NMDAR antibodies persist (1,17). Improvement of mental status may be attributed to positive effects of ECT. It has been reported that ECT may lead to significant reduction or resolution in psychiatric symptoms in anti-NMDA encephalitis, although the physiological basis for this has not been defined (18-21).

According to several authors, an initial assessment of patient presenting with first psychosis episode should include early serum and/or CSF testing for antibodies against the NMDA receptor and other antineuronal antibodies (22-24). Until now there are no well-described clinical characteristics for selection of antibody-mediated encephalitis cases; hence, the only way to detect these patients is to screen all cases with first-episode psychosis at presentation (25). Delayed diagnosis and late introduction of treatment are worldwide issues in the management of autoimmune encephalitis because of its complicated diagnostic process and the lack of pathognomonic clinical clues (26,27). The widening gap between child and adolescent psychiatry and neurology could lead to delayed diagnosis and late start of therapy in these patients with psychosis of autoimmune etiology. Initiation of treatment early in the course of the disease is proven to result in better outcomes (28,29); therefore, child and adolescent psychiatrists need to take a pro-active role in diagnosing autoimmune encephalitis when providing care for patients with first episode of acute psychosis.

Conclusions

In the reported case, anti-NMDAR- and anti-VGKC-positive encephalitis was diagnosed, and immunotherapy was introduced three months after the manifestation of psychiatric symptoms. Improvement of mental status before the start of immunotherapy occurred, and this may be attributed to positive effects of ECT. However, based on the increasing knowledge that anti-NMDAR encephalitis tends to relapse more frequently in untreated cases, intravenous methylprednisolone and IVIG were prescribed. The authors share a common concern that a widening gap between neurology and adolescent and child psychiatry could lead to delayed diagnosis and late start of therapy in the patients with psychosis of autoimmune etiology.

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All clinical work up was performed in Vilnius, Lithuania.

Conflicts of interest

The authors declare no conflicts of interest.

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