A case report of adolescent anti-NMDAR encephalitis with depressive symptoms

Depresif belirtili bir ergen anti-NMDAR ensefaliti olgu sunumu

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SUMMARY

Clinical presentation of anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis includes both neurological and psychiatric symptoms, and it is diagnosed with autoantibodies against the GluN1 subunit of NMDAR. The clinical presentation has a wide range of non-specific symptoms such as rapidly progressing psychiatric symptoms, cognitive impairment, seizures, and abnormal movements. The fact that mental and behavioural symptoms play an important role in the course of this rare clinical disorder complicates the differential diagnosis with psychiatric disorders and may lead to a delay in treatment. This case report presents the diagnostic process, treatment, and follow-up of an adolescent diagnosed with anti-NMDAR encephalitis. Neurological examination of a 15-year-old adolescent girl with sudden onset of contractions in the trunk and extremities were within normal limits when her symptoms started. Sertraline was prescribed since these were considered to be associated with new-onset depressive symptoms. She was admitted to the emergency department because of her exacerbated facial dyskinesias after using sertraline for one week. During clinical follow-up of the patient, no psychotic findings were observed, but amnesia, cognitive slowing, suicide attempts, and physical aggression were psychiatric symptoms that were difficult to manage. Psychiatric symptoms improve after switching to rituximab and regressed totally, still asymptomatic in the second year of treatment. Anti-NMDAR encephalitis usually occurs in adolescence and young adulthood. Psychiatric symptoms complicate the diagnosis. Since early intervention is a positive prognostic marker, it is important to raise clinician awareness of this particular clinical picture.

Keywords: Adolescent, anti-NMDAR, encephalitis, neuropsychiatry, psychiatric disorder, mental health, rituximab

ÖZET

Anti-N-metil-D-aspartat reseptör (anti-NMDAR) ensefalitinin klinik görüntüsü hem nörolojik hem de psikiyatrik semptomları içerir ve NMDAR'ın GluN1 alt birimine karşı otoantikorların varlığıyla teşhis edilir. Klinik görünüm hızla ilerleyen psikiyatrik semptomlar, bilişsel bozukluklar, nöbetler, anormal hareketler gibi özgül olmayan geniş bir belirti yelpazesine sahiptir. Bu nadir klinik durumun seyrinde ruhsal ve davranışsal belirtilerin önemli rol oynaması, psikiyatrik bozukluklarla ayırıcı tanısını güçleştirmekte, tedavide gecikmelere yol açabilmektedir. Bu olgu sunumunda anti-NMDAR ensefaliti tanılı bir ergenin tanı süreci, tedavisi ve takip sonuçları paylaşılmıştır. Gövde ve ekstremitelerde ani başlayan kasılmalar ile başvuran 15 yaşındaki kız ergenin nörolojik muayenesi, semptomları başladığında normal sınırlardaydı. Bunların yeni başlayan depresif semptomlarla ilişkili olduğu düşünüldüğünden sertralin reçete edilmişti. Bir hafta sertralin kullandıktan sonra fasiyal diskinezilerin alevlenmesi nedeniyle acil servise başvurdu. Hastanın klinik takibinde psikotik bulguya rastlanmadı ancak amnezi, bilişsel yavaşlama, intihar girişimi ve fiziksel saldırganlık yönetimi zor olan psikiyatrik belirtilerdi. Rituksimaba geçildikten sonra psikiyatrik semptomlar düzeldi ve tamamen geriledi, tedavinin ikinci yılında hala asemptomatikti. Anti-NMDAR ensefaliti genellikle ergenlik ve genç erişkinlik döneminde ortaya çıkmaktadır. Psikiyatrik belirtiler tanıyı karmaşıklaştırmaktadır. Erken müdahale olumlu bir prognostik belirteç olduğundan, klinisyenlerin bu özel klinik tablo hakkında farkındalığını artırmak önemlidir.

Anahtar Kelimeler: Ergen, anti-NMDAR, ensefalit, nöropsikiyatri, psikiyatrik bozukluk, ruh sağlığı, rituksimab

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INTRODUCTION

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a neuropsychiatric syndrome characterized by the presence of autoantibodies against the GluN1 subunit of NMDAR. This rare clinical disorder, first described in 2007, has significantly impacted clinical practice in neurology and psychiatry. There is a wide spectrum of symptoms that can lead to rapidly progressive cognitive impairment, mental and behavioural deterioration, abnormal movements, seizures, and in severe cases, coma (1). Anti-NMDAR encephalitis is more common in females than in males (the ratio of female to male is about 4:1). More than one-third of cases are younger than 18 years (2). Ovarian teratoma and herpes encephalitis can induce anti-NMDAR autoimmunity. Most patients present with pronounced mental or behavioural symptoms at the onset of the disorder, making it difficult to distinguish them from psychiatric disorders (1).

Data from a multicentre cohort study found that abnormal movements, seizures, irritability, and insomnia were more common in children, whereas psychosis and behavioural problems were more frequent in adults (2). Recovery from NMDAR encephalitis can take longer than 18 months. The absence of intensive care unit (ICU) admission and early treatment are considered as good prognostic markers. It has been reported that the relapse rate is 12% in the first two years, with milder symptoms than the first seizure, and relapses may occur only with psychiatric symptoms (2,3).

This case report presents a 15-year-old female adolescent with anti-NMDAR encephalitis who initially received psychiatric treatment. Our case is noteworthy because various and severe psychiatric symptoms such as suicide attempts and physical aggression improved after the administration of anti-NMDAR encephalitis-specific treatment. Although the differential diagnosis of anti-NMDAR encephalitis and psychiatric disorders is quite complex, it is important as a positive prognostic marker because of the specificity of treatment and early intervention. Therefore, the aim of this case report is to present information that should be considered in the differential diagnosis and to raise clinicians' awareness of this rare disorder.

CASE HISTORY

A 15-year-old female high school student was admitted to the pediatric emergency department complaining of aggravated facial contractions after taking sertraline (selective serotonin reuptake inhibitor-SSRI) that she had been prescribed a week ago. There was no history of mental and physical illness. The patient, who had no abnormal findings on laboratory or other systems examination, was referred to the child and adolescent psychiatry department for a differential diagnosis of conversion disorder (functional neurological symptom disorder).

Detailed history revealed that the patient had numbness in her lips for 3 months, contractions on the right side of her body for 1 month, and her mouth was shifted to the right. Neurological examination, EEG, and cranial magnetic resonance imaging (MRI) performed at the time of the onset of contractions was within the normal range. The past medical and family history was negative for epilepsy. The patient, who suffered from mood swings, episodes of excessive crying and becoming more emotional, and obsessions for 1 month, was referred to the child and adolescent psychiatry department one week ago. With a diagnosis of depression sertraline 25 mg/day was recommended. After taking sertraline, the contractions in the extremities ceased, but the contractions in the face exacerbated. During the examination, the questions could only be partially answered by the patient because of the contractions in her face. Her orientation and thought content could not be assessed because she had difficulty speaking and could not fully answer the questions. There was no delay in her developmental stages, and she had a moderate academic performance. During the psychiatric interview, it was observed that her symptoms were becoming more severe and without any diminution. Since conversion disorder was not considered in the first place, consultation with a pediatric neurologist was recommended.

On neurological examination, the patient hand synkinesis around the mouth and cortical diffusion

restrictions, which were thought to be due to seizures on cranial MRI. EEG showed paroxysmal delta activity in wakefulness and epileptogenic potentials in anterior regions during sleep. The patient was treated with phenytoin and levetiracetam for the seizures. With a preliminary diagnosis of autoimmune encephalitis, the patient underwent lumbar puncture and an autoimmune encephalitis panel of blood and craniospinal fluid (CSF), a paraneoplastic panel (chest-abdominal-pelvis MRI, tumor markers), and inflammatory markers of CSF/blood were examined (anti-MOG, oligoclonal bands, IgG index). The patient was started on methylprednisolone pulse therapy of 1 g/day. Intravenous immunoglobulin (IVIg) 2 g/kg was administered for two days. After the anti-NMDAR antibody level in the patient's CSF was positive, the patient was diagnosed with anti-NMDAR encephalitis. The patient's seizures stopped on the second day of treatment with methylprednisolone and IVIg, and her EEG was normalized on the twentieth day of treatment. Since anti-NMDAR antibody positivity in CSF and serum persisted into the fourth month of treatment, monthly IVIg pulse steroid treatment for another year was planned. During this time, the patient's seizures did not recur, but psychiatric symptoms were found to play an active role in the clinical picture.

At the sixth month of treatment, the patient, whose aggressiveness, thoughts of death, and depressed mood persisted, was referred to the child and adolescent psychiatry clinic for mental status evaluation. She had trouble falling asleep. She had amnesia. There was a suicide attempt by jumping out of a window and physical violence towards others, but she was amnestic about these incidents. Past history was irrelevant for alcohol or illicit drug use, she had no traumatic experience, and she was free of psychotic symptoms. She failed at school due to difficulties in learning. The Children's Depression Inventory (CDI) score was 23 (cut-off score for depression 19). The sentence completion test included themes of suicide and running away from home. A few weeks after this mental examination, the patient developed left sided focal seizures and sleep disturbances, the EEG showed frequent epileptogenic potential in both anterior regions of the left hemisphere. The patient was accepted as relapsed, and she was treated with 5 doses of plasmapheresis following 5 days. Subsequently, treatment with rituximab was started. The patient's symptoms, treated twice with rituximab six months apart, stabilized and the seizure did not recur.

At the end of the first year of treatment, her mood was euthymic, sleep patterns and appetite were normal. There were no amnesia, irritability, aggression, suicidal ideation, or psychotic findings. Her depressed mood improved significantly, and the last CDI score was 6, in the sentence completion test, there were common themes related to daily life in accordance with her developmental level. Her academic performance improved gradually.

The patient, who has been under follow-up for two years, continues to be treated with rituximab and she was medically stable without any psychiatric symptoms. Informed consent was received from her and her family regarding this case report.

DISCUSSION

We present a case of anti-NMDAR encephalitis in an adolescent treated with a previous diagnosis of depression whose clinical symptoms worsened after taking SSRIs, as MRI and EEG were within normal limits when symptoms appeared. Literature reports that psychotic symptoms are generally observed with anti-NMDAR encephalitis. In one case report, depressive symptoms were found without psychotic symptoms (4).

The manifestation of symptoms in anti-NMDAR encephalitis varies between children and adults. Facial dyskinesias, which occur in about 75% of adults and 95% of children, and various abnormal movements involving the extremities and trunk are common manifestations of anti-NMDAR encephalitis and valuable clues for recognizing the disease (1,2). These patients may have oral, facial, or lingual dyskinesias, chorea, athetosis, dystonia, opisthotonos, and blepharospasm (5,6). While neurological symptoms dominate the general clinical picture in children, psychiatric symptoms play a substantial role in adults. However, with the progression of symptoms, the clinical picture evolves into a similar syndrome in all age groups after a few weeks (2). The symptoms of our case, a 15-year-old

female adolescent, progressed as expected due to early age of presentation, with mood symptoms appeared later in the course. As the initial neurological assessment for sudden onset of symptoms was within the normal range, the treatment plan was targeted to treat mood changes. In this context, it is noteworthy that psychiatric symptoms play a central role in the differential diagnosis of anti-NMDAR encephalitis cases. In one study, psychiatrists were found to be involved in the diagnostic process in three-quarters of these patients (5). Lejuste et al showed that about half of the cases were initially referred to a psychiatry clinic (7). Recognition of this symptom cluster should suggest clinicians to test for antibodies against the GluN1 subunit of NMDAR (2).

Although there are no specific guidelines for managing psychiatric symptoms in patients with anti-NMDAR encephalitis, it is generally recommended to provide symptomatic treatment and to weigh the cost-benefit ratio, as unexpected side effects such as intolerance to neuroleptics may occur in these patients (7). In addition, it has been reported that new-onset psychiatric symptoms during follow-up of patients with a history of anti-NMDAR encephalitis may signify a clue for a relapse (3).

To conclude, in this case report, we would like to emphasize the importance of carefully considering medical causes when evaluating and treating psychiatric disorders. Furthermore, we believe that multidisciplinary follow-up is the most important strategy to achieve the best clinical outcome in encephalitis cases.

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