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LETTER TO THE EDITOR

Management of neuropsychiatric symptoms in anti NMDAR encephalitis: a case report

Anti NMDAR ensefalitinde nöropsikiyatrik semptomların yönetimi: olgu sunumu

Fatma Subaşı Turgut[1], Ayşe Aysima Özçelik[2], Hasan Kılıç[2], Mehmet Karadağ[2]

[1]Dicle University, Diyarbakır, Türkiye
[2]Gaziantep University, Gaziantep, Türkiye

To the Editor,

Anti-N-Methyl-D-Aspartate Receptor (NMDAR) encephalitis is recognized as the most commonly diagnosed autoimmune encephalitis and is one of the most common causes of encephalitis[1]. NMDAR encephalitis is increasingly recognized in children, accounting for 40% of all cases[2]. NMDAR antibodies were initially described in association with a purely paraneoplastic panencephalopathy in young female patients with an underlying ovarian teratoma[3]. However, subsequent studies have shown that these antibodies are predominantly associated with a nonparaneoplastic disease and that both adult men and children are also commonly affected[1]. Symptoms include a highly characteristic set of neurological deficits, but also include a wide range of psychiatric manifestations[4]. Early recognition and prompt initiation of immunotherapy improves outcomes[5].

Our case was a 16-year-old female adolescent with no previous medical or psychiatric history. She had been experiencing forgetfulness, weakness and fatigue for 1-2 weeks. After these complaints, she had a 1-2 minute seizure with convulsions in the whole body. On admission, she complained of loss of strength, talking to herself, laughing at the walls, looking around with frightened eyes, urinary incontinence, not eating, and not sleeping. EEG showed delta brush activity in both the frontal and frontotemporal regions (Figures 1 and 2).

Cerebrospinal fluid (CSF) pressure was normal on the lumbar puncture; no cells were observed in the CSF; cytology was normal; no growth was observed in culture; and viral agents were reported as negative. Serology results for systemic autoimmune diseases were negative. Tumor markers were within normal limits. Pelvic and abdominal USG and abdominal CT showed no pathology. MRI of the brain showed mild thickening of the dural surfaces, marked inflammation at the level of the vertex and mild diffusion restriction on diffusion imaging. The anti-NMDAR antibody was positive in cerebrospinal fluid, and the patient was diagnosed with anti-NMDAR encephalitis.

Steroids could not be administered in the first stage due to the high CRP value of the patient. Therefore, IVIG was given at a dose of 0.4 mg/kg/day for 5 days. After the CRP value returned to normal, steroid administration was started at a dose of 30 mg/kg/day and continued for 5 days. In the psychiatric evaluation, the patient displayed poor self-care, avoided eye contact, did not engage in verbal communication, and was not receptive to interaction. Her mood was irritable, her affect was fluctuating, and her consciousness was cloudy. Since the patient did not speak, perception and thought content could not be evaluated, but looking around with fearful eyes, looking at the wall and laughing, whispering something as if talking to herself, and gesticulating as if someone were present were considered psychotic findings. Total sleep time decreased to 2-3 hours a day. She refused to eat. Wax elasticity, catalepsy, agitation, mutism, and grimacing were found on examination. There was no period of complete

Address for Correspondence: Fatma Subaşı Turgut, Department of Child and Adolescent Psychiatry, Faculty of Medicine, Dicle University, Diyarbakır, Türkiye E-mail: fsubasiturgut@gmail.com
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resolution of symptoms. Catatonia due to organic pathology was considered. Lorezapam 2.5 mg was started and gradually increased to 7.5 mg/day. Significant improvement was noted in insomnia, aggression, and agitation after lorezapam treatment. Plasmapheresis was initiated because of an inadequate response to IVIG and steroid treatment.

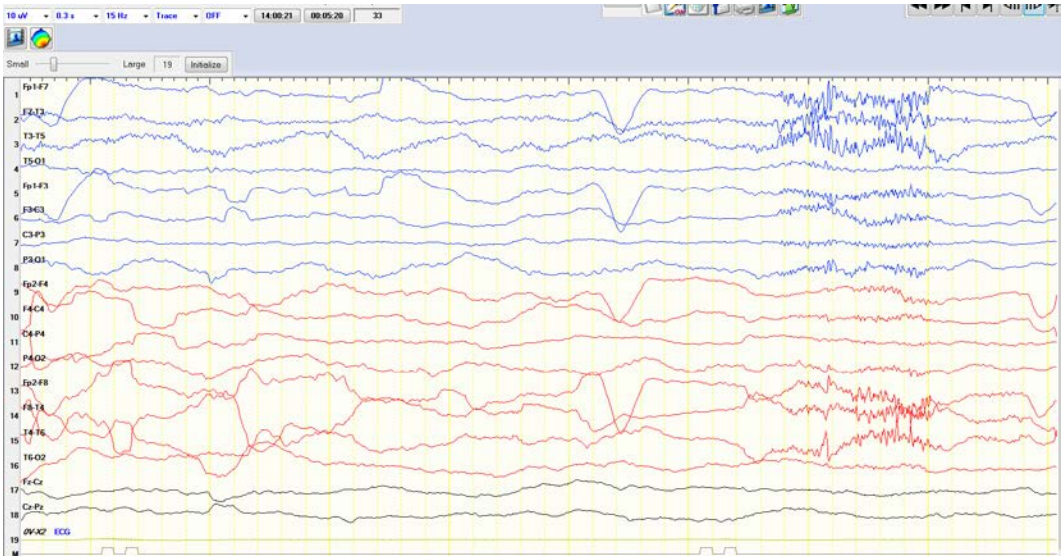

Figure 1. The delta-brush activities in the patient's EEG.

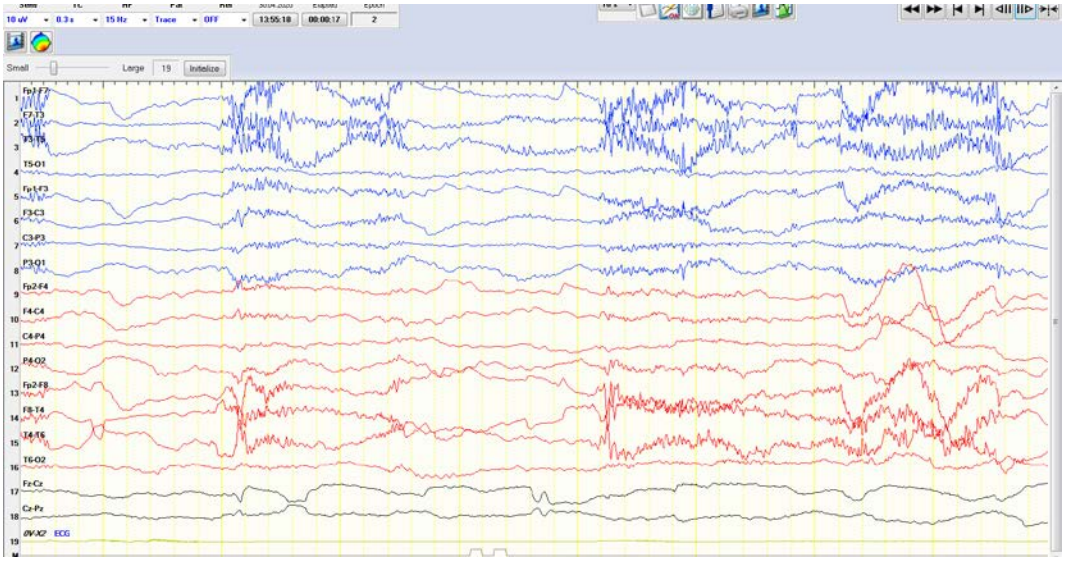

Figure 2. The delta-brush activities in the patient's EEG.

During the first week of plasmapheresis treatment, the patient could not be communicated with. The patient was constantly trying to keep the door of the room closed, closing the curtains, hitting the mother, crying for no reason, hiding his cell phone under the pillow, and talking to herself. Urinary incontinence

improved after plasmapheresis. The patient started to recognize her mother after receiving plasmapheresis for the fifth time. She started to obey simple commands and hold a pencil. The patient was asked to draw a clock to evaluate motor and copying skills (Figure 3 A drawing). When communication was started with the patient, it was realized that she had both retrograde and anterograde amnesia. At the start of the conversation, he started to express his persecution delusions. After the 7th plasmapheresis, psychotic symptoms and amnesia still persisted. When the patient was asked to draw a clock again, there was no significant improvement in motor skills (Figure 3 B drawing). Rituximab 375 mg/m2 was started after plasmapheresis failed to elicit an adequate response. Four doses were given in weekly doses. Irritability, irritability, and amnesia partially persisted at the end of Rituximab treatment. There was a significant improvement in psychotic symptoms, motor skills, and copying skills (Figure 3 C drawing).

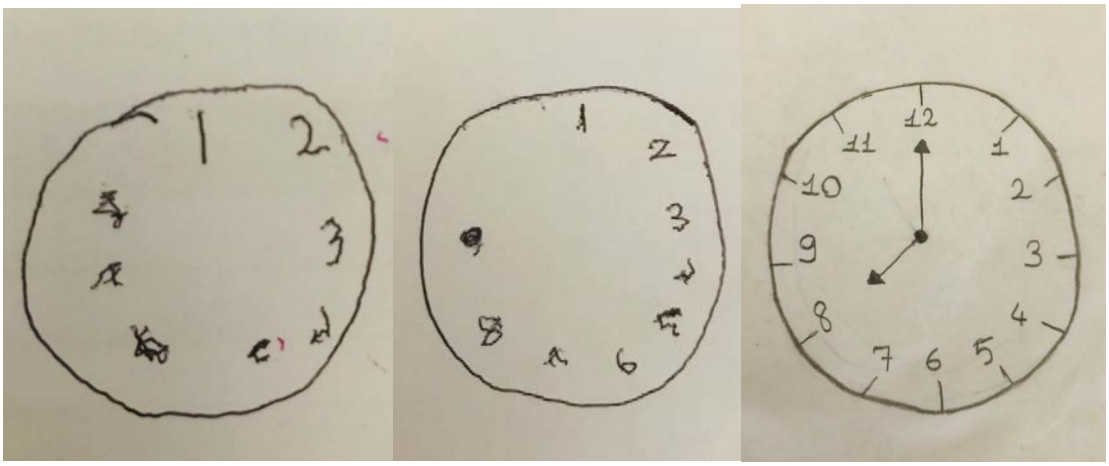

Figure 1. Clock drawings of the patient in 3 different periods

When the patient was discharged on the 40th day of hospitalization with outpatient follow-up planned, some cognitive problems, amnesia, and motor function problems partially persisted.

Anti NMDAR encephalitis has a wide range of symptoms including psychosis, catatonia, behavioral and memory changes, seizures, abnormal movements and autonomic dysregulation and requires a multidisciplinary treatment approach[1].

Seizures can occur at any point, including the onset of the disease, and especially seizures without fever should alert clinicians to antibody-associated encephalitis[6]. Our patient's seizure after a short prodramal period and the absence of fever during follow-up supported the diagnosis of antibody-associated encephalitis.

In anti NMDAR encephalitis, EEG changes associated with encephalitis can be seen in the majority of patients. The extent of EEG abnormalities has been shown to correlate with the clinical severity of anti-NMDAR encephalitis[7]. A unique electrographic pattern called "excessive delta brush" has been described in anti NMDAR encephalitis. The presence of excessive delta brush has been associated with worse prognosis and longer hospitalization[7]. Considering that the results of autoantibody tests take a long time, excessive delta brush on EEG in patients presenting with seizures and neuropsychiatric symptoms may be a warning sign for autoimmune encephalitis and may have prognostic significance. However, in our case, despite excessive delta brush waves on EEG, the prognosis was good contrary to the literature. Early diagnosis and early initiation of second-line therapies may have contributed to this.

A characteristic feature of patients recovering from anti-NMDA-receptor encephalitis is a persistent amnesia throughout the whole process[6]. This symptom is consistent with disruption of synaptic plasticity mechanisms in learning and memory, in which NMDA receptors play an important role[3]. The first finding in our case was amnesia, which persisted throughout the whole process and was still

continuing at the 3rd month after the onset of the disease.

In the literature, psychiatric symptoms such as psychosis and catatonia are very common in patients with anti-NMDAR encephalitis, and even isolated psychiatric episodes have been reported[4]. Screening for NMDAR antibodies may be useful in psychosis, catatonia or affective symptoms associated with neurologic symptoms, or in isolated psychiatric episodes unresponsive to psychiatric treatments.

In anti NMDAR encephalitis, both typical and atypical antipsychotics are used alone or in combination to manage psychiatric symptoms[8]. Typical antipsychotics, especially high-potency dopamine antagonists such as haloperidol, may cause extrapyramidal symptoms and worsen motor symptoms, which may worsen agitation[9]. While benzodiazepines remain the first choice to treat catatonic symptoms, they help with sleep and are also helpful in the prophylactic treatment of seizures[8]. Consistent with the literature, lorezapam was effective in treating insomnia, agitation and catatonic symptoms.

About half of patients with anti-NMDAR encephalitis improve with immunotherapy, including high-dose intravenous corticosteroids and intravenous immunoglobulins, but patients who do not improve with first-line therapies should be treated with second-line agents such as rituximab or cyclophosphamide[10]. In patients with tumors, the response rate to tumor removal and first-line treatment is approximately 80%, while in patients without tumors, the response rate to first-line treatment is 48%[1]. Pediatric patients are less likely to have associated tumors, which may contribute to the failure of first-line immunotherapy in up to half of all children treated for anti-NMDAR[5]. Rituximab, a monoclonal antibody, has been successfully used in the treatment of anti-NMDA receptor encephalitis and early initiation accelerates the recovery of patients with anti-NMDAR encephalitis[10]. After no significant response to IVIG, intravenous corticosteroids and plasmapheresis, our patient was treated with Rituximab and the clinical recovery process was accelerated. The patient's motor skills and cognitive functions improved dramatically after Rituximab.

Early diagnosis of encephalitis, which has a high mortality and morbidity rate, is crucial to ensure timely and appropriate treatment. Given that early diagnosis and treatment can significantly improve neuropsychiatric symptoms, it is crucial for clinicians to be aware of NMDAR encephalitis and consider it in differential diagnoses.

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